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Intramural Depolarization Potentials in Myocardial Infarction

A Preliminary Report

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By means of small intramural electrodes, potentials at multiple depths within the ventricular wall were recorded in myocardial infarction and in normal hearts. In 41 animals with coronary artery occlusion, electrocardiographic and histologic correlations indicated that coronary QS waves may represent negative potentials transmitted from viable intramural muscle as well as from the cavity. Coronary QR waves were obtained over transmural infarcts containing a mixture of viable and dead tissue, but not over purely subendocardial lesions. In the normal ventricle, positive depolarization potentials greatly predominated over negative potentials. Clinical applications are discussed.

THE MOST SIGNIFICANT electrocardiographic feature of myocardial infarction is the presence of a surface QS or QR wave, either of which is believed to indicate myocardial death. In view of their clinical importance, these pathologic signs warrant more thorough experimental investigation than has been reported to date. Current theories concerning the origin of QS and QR waves are derived entirely from studies of potentials on the ventricular surfaces and in the ventricular cavities; potentials within the myocardium, or what may properly be called "intramural" potentials, have been recorded previously on rare occasions[1-3] but never in myocardial infarction.

In the present study, new evidence regarding intramural activity is being obtained by means of a "plunge" electrode which makes it possible to record tracings from minute areas within the ventricular wall. This specially designed electrode, in conjunction with cinematoelectrocardiographic and histologic examination of the ventricles, has been employed thus far in a total of over 100 dogs with normal cardiac function or with experimentally produced myocardial infarcts, bundle branch block, ventricular extrasystoles or tachycardia. The following preliminary report is concerned primarily with the relationship between intramural and epicardial depolarization potentials as observed in 41 instances of myocardial infarction. In addition, the distribution of potentials within the normal ventricle is described in order to explain certain findings associated with abnormal surface Q waves. Intramural studies of bundle branch block and ventricular arrhythmias, as well as additional observations on normal and infarcted ventricles, will be reported in subsequent communications.

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Materials and Methods

Myocardial infarcts were produced in 41 dogs by ligating the left anterior descending coronary artery about halfway down its course. An interval varying from two days to five months followed the initial operation, after which each animal was reanesthetized and routine limb and precordial tracings were made. The chest was then opened, artificial respiration maintained with an electric pump respirator, and the heart widely exposed by an incision described elsewhere.[4]

Electrocardiographic Equipment and Technic

Intramural and cavity leads were recorded by "plunge" electrodes made of tempered silver the diameter of a fine needle and insulated throughout their length except at the chloride-coated tip which formed the recording surface. Effort was made to minimize the size of the recording surface so that it would register potentials from highly localized points. Each electrode was accurately marked at 5 mm. intervals; when the electrode was plunged into the myocardium, the markings made it possible to determine the depth of the tip within 1 to 2 mm. Epicardial leads were recorded from a cotton electrode with a somewhat larger surface than that of the plunge electrode.

In each animal, a plunge electrode was introduced into the cavity of the exposed left ventricle; this lead was used as a reference and was recorded simultaneously with epicardial or intramural leads from selected sites. As many as four or five plunge electrodes were used in each heart, and intramural tracings from each electrode were taken at several measured depths from the surface. Current of injury, caused by insertion of the plunge electrode, normally attained a minimum after about five minutes. Epicardial and intramural tracings were obtained from normal control tissue as well as from the margins and central portions of the infarct. The position of all electrodes was verified post mortem.

The possibility that the presence of a plunge electrode might induce focal block in the surrounding myocardium, thereby rendering the intramural tracings unreliable, was investigated by the following simple experiment: A cotton electrode was fixed to the epicardial surface of the ventricle. The plunge electrode was then inserted obliquely into the ventricular wall so that its recording tip lay in the myocardium almost 1 mm. beneath the surface electrode. If perifocal block, or any other depolarization abnormality, were induced by the plunge electrode, simultaneous tracings from the surface and intramural electrodes should be dissimilar; that is, the abnormality would be recorded by the plunge electrode and not by the surface electrode. It was found, however, that the depolarization waves recorded simultaneously from the two electrodes were practically identical in almost every instance except that, as expected, the R wave in the intramural lead was slightly lower than the surface R wave. The width of the QRS complexes of both leads was identical, thus demonstrating the absence of block in the region of the intramural electrode. Indeed, in all experiments subsequently performed on normal hearts, the depolarization complexes in simultaneous cavity, intramural and epicardial leads were always of equal width. On the rare occasions when perifocal block or other abnormalities were caused by the plunge, they were recognized without difficulty and always disappeared after a short interval or after reinsertion of the electrode.

In order to determine whether the electrodes registered primarily local potentials, a variety of experiments was performed. For example, in normal tracings from epicardial or plunge electrodes situated a short distance from the auriculoventricular groove, the P wave usually was absent or very small. The plunge electrode was further tested by recording intramural leads from one ventricle before and after the entire contralateral ventricle was cut away; little or no change in the deflections registered by the electrodes was noted. In bundle branch block, on the other hand, plunge electrodes in the blocked ventricle often recorded deflections 2 to 3 mm. in amplitude, representing electrical activity in the opposite unblocked ventricle. It was thus demonstrated that the electrodes registered predominantly, although not exclusively, local events. This conclusion may be reached on theoretic grounds by application of Poisson's integral which states that the electromotive force is inversely proportional to the cube of the distance between the electrode and the depolarizing cell.[5] The potentials of cells in immediate contact with the recording tip therefore affect an electrode many times more forcibly than potentials as little as a few millimeters distant from the tip.

All electrocardiograms were registered on a Brush recorder operated at a paper speed of 125 mm. per

second. This rapid paper speed yields deflections five times broader than those in standard tracings, thereby greatly facilitating examination and comparison of depolarization waves. Power was supplied through the amplifying system of a Sanborn Polyviso. The indifferent electrode was connected to Wilson's central terminal for all experiments. All direct leads were recorded at × 20 attenuation with the sensitivity adjusted so that 20 millivolts corresponds to a 15 mm. deflection. Although actual comparative tests have shown that the Brush Recorder is less sensitive than oscillographic equipment, the former was found to be completely satisfactory for the present study.

Cinemato-electrocardiographic Technic

In 19 of the 41 instances of experimental myocardial infarction, the motion of the left ventricle was photographed simultaneously with direct epicardial or intramural leads. This recently developed technic is described in detail elsewhere.[6] By recording at fast camera speeds under high magnification, the precise movements of ventricular muscle associated with a specific electrocardiographic pattern can actually be visualized. Thus the cinematoelectrocardiographic technic yields a close correlation between mechanical and electrical events in the ventricle.

Histologic Examination

After the desired electrocardiographic and cinematographic observations had been made, the experimental animals were sacrificed and relevant portions of the heart subjected to careful histologic study. The plunge electrodes were left in situ until after the tissue was carefully cut, fixed, and prepared for the microtome. Microscopic examination of the stained sections often revealed clearly the tracts made by the plunge electrodes. Since the intramural tracings had been recorded at measured distances from the epicardial surface, it was thus possible to identify the precise bit of tissue from which each tracing was derived. All epicardial, intramural and cavity electrocardiograms obtained during the experiments were appropriately located on an enlarged microphotograph of the section, allowance being made for shrinkage of tissue. The microscopic findings were then correlated with the cinematographic and electrocardiographic data.

Intramural Potentials in the Normal Ventricle

By the "plunge" technic described, 35 observations on intramural potentials at various depths of the free ventricular walls were made in 23 dogs with normal hearts. On eight occasions, normal potentials were recorded from various depths of the left papillary muscle. Since the right papillary muscle is smaller and less accessible than its counterpart, investigation of the former was not undertaken. Finally, in 14 normal ventricles, electrical activity throughout the septum was recorded with a specially designed electrode. The results of these studies are summarized here because of their pertinence to the subsequent discussion of myocardial infarction.

The Free Ventricular Walls

Consistently, a rapid diminution in the size of the R wave and a striking growth of the S wave occurred as the electrode was plunged deeper into the wall of the normal ventricle (fig. 1). In some tracings from as little as 3 mm. below the epicardial surface, the R wave was absent or almost indistinguishable and a deep S or QS wave appeared. In the majority of animals, the inner half of the wall of both ventricles yielded pure QS deflections. Findings in the left and right ventricular walls were similar, except that the outer zone of positivity appeared to involve a greater proportion of the right ventricle than of the left.

The phenomenon of negativity within the normal ventricular wall was further explored by eliminating all or part of the outer zone of positivity. Portions of the epicardium and underlying muscle were severely burned in 23 dogs and actually excised in five dogs, after which the surface was subjected to electrocardiographic study. When compared with leads from the normal surface, tracings from the burned epicardium or newly exposed muscle consistently exhibited marked lowering of the R waves. In five instances the R wave was completely replaced by a pure QS wave. These findings confirm the results obtained by Bellet and Johnston,[3] who produced similar burns and recorded potentials from the new surface and immediately subjacent tissue.

Intramural potentials recorded from all depths of the left papillary muscle in normal hearts were consistently negative. However, an embryonic R wave or slur was often distinguished at variable points on the downstroke of the QS wave. The intramural deflections recorded from the left papillary muscle were of

greater amplitude than those from the neighboring cavity.

The Interventricular Septum

The septum was explored with a curved electrode which was slightly thicker than the plunge electrode, composed of the same tempered silver, and insulated throughout its length except for a segment of about 1 mm. in the middle which formed the recording surface. By passing this electrode through the heart from one ventricular surface to the other, it was possible to record successively from one cavity, from the adjacent septal surface, from various points within the septum, and finally from the opposite septal surface and adjacent cavity. Current of injury always appeared when the electrode was pushed into the septum; this phenomenon served to localize the position of the electrode, since no current of injury occurs in cavity leads.

As the septum was traversed from right to left, the following sequence of electrocardiographic events was observed: A small R wave followed by a deep S wave was recorded from the right septal surface. The R wave grew larger as the electrode was drawn deeper into the septum, attaining maximum amplitude in tracings from approximately halfway between the left and right septal surfaces. Subsequent tracings showed a progressive diminution in the size of the R wave until, when the electrode neared the left septal surface, the R wave disappeared and was replaced by a QS deflection.

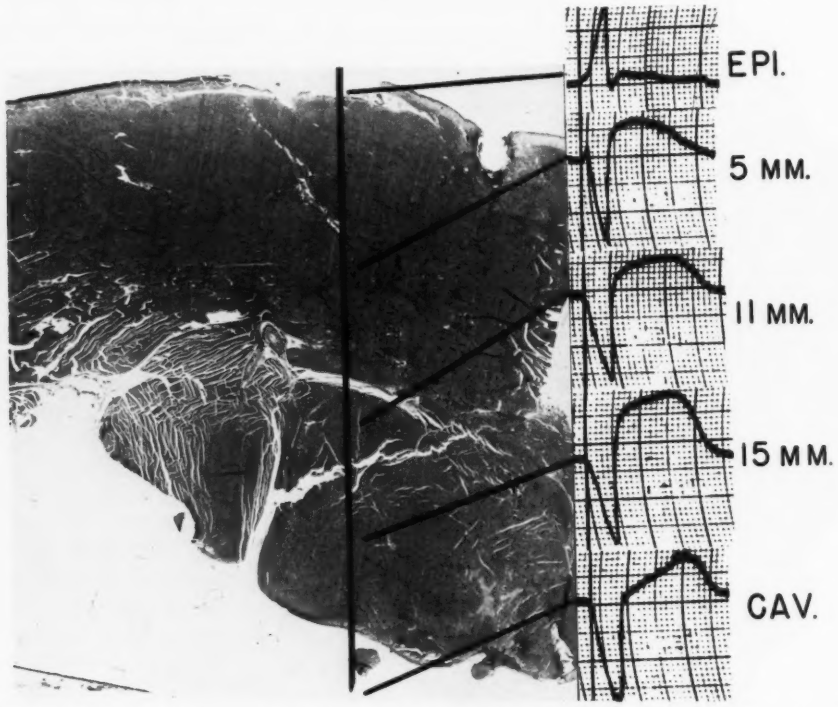

FIG. 1. Epicardial, intramural and cavity leads from normal left ventricle of dog. Magnification ×6.2. Tracings recorded at 125 mm. per second paper speed, attenuation ×20. Sensitivity: 20 mv. equal 15 mm.

In tracings recorded 5 mm. below surface, the R wave is small and is followed by a large S wave. Muscle 11 or 15 mm. below the surface yields no R wave. Hence it appears that positive potentials normally prevail only at and immediately beneath the surface of the ventricular wall. S-T segment elevation indicating current of injury is due to trauma by plunge electrode.

As the left cavity was entered, current of injury vanished and the QS wave persisted. These findings support the concept that most of the septum is actually a part of the left ventricle.[7]

Comment

The striking feature observed in intramural studies of the normal ventricles is the unexpected predominance of negative over positive potentials. With the exception of a relatively thin shell on the epicardial surface and in the middle and right side of the septum, all portions of the ventricular musculature yielded essentially negative deflections. Predominantly positive depolarization potentials were found to prevail in only about 20 per cent of the ventricular muscle of the normal heart. In contrast, when an impulse traverses a two-dimensional muscle strip, 50 per cent of the tissue yields predominantly negative deflections and the remaining 50 per cent is predominantly positive. Hence the ventricular myocardium apparently does not behave electrically in the same manner as a simple muscle strip. The distribution of potentials in the auricles, on the other hand, is consistent with the behavior of a simple muscle strip.[4, 8]

Until more is known concerning the electrophysiology of cardiac muscle, the apparent difference in mode of auricular and ventricular depolarization cannot be adequately explained. Among the factors which may be pertinent are: (1) The auricular wall is sufficiently thin to act electrically as a two-dimensional structure, while the thicker ventricle must undergo three-dimensional depolarization.* (2) The auricles possess no specialized conducting tissue, whereas the Purkinje system penetrates deeply into the ventricular wall. Hence the depolarization wave may enter the ventricular myocardium at a relatively superficial intramural level rather than at the endocardium. (3) The auricular depolarization wave travels at a constant rate of speed. The velocity of the ventricular depolarization process, as determined in the present study by comparing the times of onset of the intrinsic deflections in leads from multiple intramural levels, is greater in the inner half of the ventricular wall than in the outer portion. This finding may be related to the penetration of the Purkinje system into the ventricular wall, or to as yet undiscovered biochemical and/or enzymatic differences within the ventricular myocardium.

* This conclusion is supported by unpublished observations on the spread of the ventricular excitation wave in experimental bundle branch block, ventricular extrasystoles and tachycardia. Positive depolarization potentials were found to prevail throughout the blocked ventricle during bundle branch block, and throughout the contralateral ventricle during extrasystoles or tachycardia originating from a focus on either ventricle.

The Coronary QS Wave

Current concepts concerning the significance of the coronary QS wave are based primarily upon the experimental studies of Wilson and his associates.[9] These workers found that regions of transmural infarction, whether acute or chronic, yielded almost identical QS waves in leads from the epicardial surface and the subjacent cavity. Furthermore, pressure on the epicardium failed to elicit current of injury in surface leads. As interpreted by most commentators, Wilson's fundamental findings signify that the negative potential of the cavity is passively transmitted unaltered through a transmural "hole" or "window" of infarcted tissue. Thus, epicardial or precordial QS waves generally are believed to occur over regions of through-and-through muscle death.

Thirty-five of the 41 instances of experimental myocardial infarction included in the present study were shown histologically to involve tissue at all levels from the ventricular cavity to the epicardial surface. A correlation of observations in these transmural lesions indicates that two types of QS waves may be recorded from the surface of either acute or chronic infarcts. The first type of surface QS wave appears to be derived entirely from the negative cavity potential, as suggested by Wilson, and may therefore be called the cavity type of surface QS wave or, more conveniently, the surface "QSc" wave. The second type of surface QS wave evidently is at least partially determined by electrical activity in the ventricular wall; hence it will be tentatively termed the mural type of surface QS wave, or simply the surface "QSm" wave. The distinctly dif-

ferent pathologic situations responsible for "QSc" and "QSm" waves have been demonstrated by three methods: (1) Cinematographic and electrocardiographic exploration of the epicardium; (2) intramural leads from multiple levels, and (3) histologic examination of the infarcted region.

Cavity-Type QS (QSc) Surface Wave

1. Cinematographically, epicardial regions yielding QSc waves were seen to protrude or balloon while normal portions of the ventricle were in systole. This phenomenon, most apparent in profile views of the heart and in lesions of relatively recent origin, indicates absence of contraction of the infarcted area.[10] Electrocardiographically, the entire ventricular complex including the surface QSc wave was identical in timing, magnitude and configuration with simultaneously recorded cavity leads. The QS waves in both epicardial and cavity tracings exhibited early onset and gently rounded contour; the S-T segments were always isoelectric and failed to show current of injury when the surface was traumatized by pressure with a sharp electrode or by application of a 10 to 15 per cent solution of potassium chloride; the T waves were slightly positive and did not change when the surface of the infarct was heated. Further evidence of muscular inactivity was obtained by stimulating the QSc area with a sharp applicator or with an interrupted current of threshold intensity; no response occurred, although either of these procedures consistently elicits extrasystoles when applied to normal ventricular muscle.

2. Intramural tracings from various levels of regions yielding surface QSc waves consistently exhibited ventricular complexes indistinguishable from those in epicardial and cavity leads. Furthermore, when the cavity potential was deliberately altered as by the production of bundle branch block, the intramural and epicardial tracings promptly registered changes identical with those in the cavity lead. Finally, at no time was a current of injury elicited by insertion of the plunge electrode into the substance of the infarct, although extreme elevation of the S-T segment always is observed when these electrodes are plunged into normal muscle. Failure to produce injury current at any level of an infarct from epicardium to endocardium appears to constitute definitive evidence of uniform through and through muscle death.

3. Histologic examination of infarcted regions yielding surface QSc waves showed complete loss of normal muscle. From epicardium to endocardium, the region consisted of a homogeneous scar of necrotic or fibrotic tissue, depending upon the age of the infarct (fig. 2).

The preceding observations confirm and supplement the work of Wilson. In transmurally infarcted regions devoid of viable muscle, the negative depolarization potential recorded at the surface must be transmitted unmodified from the subjacent cavity. Hence the cavity type of surface QS wave completely conforms to accepted theory concerning the genesis of the QS wave of myocardial infarction.

Mural-Type QS (QSm) Surface Wave

1. Cinematographs of the surface of infarcts yielding QSm waves unexpectedly revealed distinct muscular activity. In at least four such lesions, each older than 11 days, active contraction was demonstrated by outlining the QS area with Janus green; the outlined region was clearly seen to wrinkle and shrink during ventricular systole. A number of infarcts exhibited systolic contractions of QSm areas at the periphery, while QSc areas over the center of the lesion showed characteristic ballooning.

Surface electrocardiograms containing QSm waves differed from leads exhibiting QSc waves in several significant respects: (*a*) Mural-type surface QS waves often were readily distinguished from the QS wave in simultaneously recorded cavity leads; the former frequently started later, presented a more abrupt downstroke, were sometimes deeper, exhibited a sharp tip, and occasionally were notched by the presence of a small embryonic R wave or merely by a slight slur. These differences between surface and cavity deflections must represent the electrical activity of surviving muscle within the infarcted region. (*b*) Elevated S-T segments following QSm waves, indicating current of injury, frequently occurred spontane-

ously in infarcts of less than two or three days duration, and could be produced in older lesions by mechanical or chemical trauma. (*c*) The T waves in surface leads containing QSm waves usually were higher than those in simultaneous cavity leads and increased in amplitude when the infarct was heated. Neither current of injury nor T-wave changes could be produced by dead muscle. The presence of viable muscle was further demonstrated by the frequent occurrence of extrasystoles when surface regions yielding QSm waves were stimulated with a sharp applicator or an electric current.

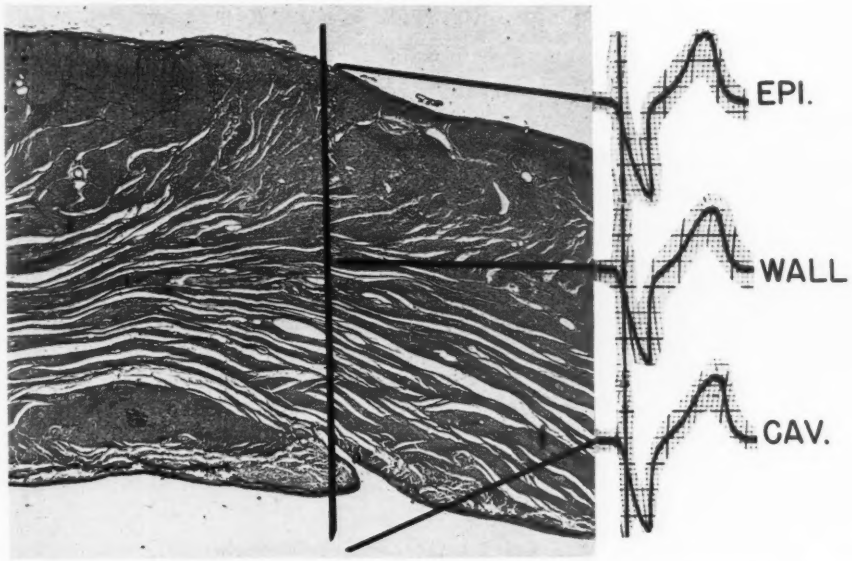

FIG. 2. Epicardial, intramural and cavity leads taken in region of through-and-through infarction. The infarct is 13 days old and is magnified 23 times. Arrow shows approximate location of plunge electrode. All tissue is fibrotic.

As shown by microscopic examination of section and by failure to elicit current of injury at any level, no viable muscle remains within infarcted region. Note that cavity-type QS deflection recorded from the surface is identical with QS waves from the middle of the wall and from the cavity. The negative potential clearly is transmitted unaltered from the cavity through dead muscle to the surface. In the absence of viable intramural muscle, the surface QS wave could have no source other than the cavity.

2. Intramural muscle directly subjacent to surface regions yielding QSm waves also showed unmistakable evidence of electrical activity. In tracings from these regions, the intramural QS waves differed in size, shape and magnitude from QS waves recorded at other intramural levels, from the simultaneously recorded cavity QS wave, and from the surface QS wave. If the surface QS wave were transmitted from the cavity through uniformly dead tissue, it would scarcely assume such diverse appearances during the course of its journey. Furthermore, S-T segment elevation consistently occurred when the plunge electrode was introduced into regions presenting surface QSm waves; this phenomenon indicated current of injury resulting from trauma by the electrode in chronic infarcts, and from trauma combined with spontaneous reaction of the freshly infarcted tissue in acute lesions.

3. Histologically, regions of transmural infarction presenting the mural type of surface QS wave were found to include irregularly dispersed islands of surviving muscle surrounded by areas of necrotic tissue in recent infarcts and by fibrotic scar tissue in older lesions. Both

the location and the quantity of surviving muscle varied in different infarcts. Occasionally, certain layers of the myocardium consisted entirely of necrotic or fibrotic material, but patches of surviving muscle tissue always were present at some levels of infarcted regions from which surface QSm waves had been recorded during life (fig. 3).

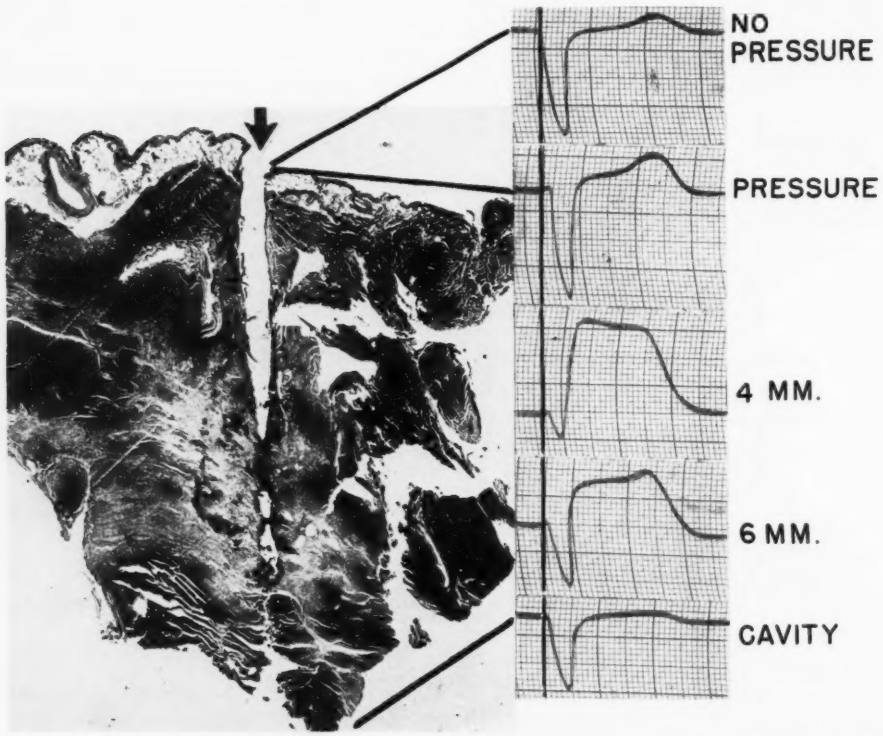

FIG. 3. Electrocardiographic and histologic appearance of section of left ventricle with 17 day old infarct. Fibrous tissue appears white or grayish-white, surviving muscle dark grey or black. Path left by plunge electrode is shown by arrow. Magnification ×10.

Surface QS wave appears superficially similar to the QSc deflection in figure 2. However, current of injury obtained in surface lead upon application of pressure, and at intramural levels establishes presence of viable muscle within infarcted region. Note that QS waves in leads from surviving muscle 4 mm. and 6 mm. below surface differ from surface QS wave as well as from cavity QS. These findings indicate that surface QS deflection is of mural type (see text).

The preceding histologic findings provide an anatomic basis for the mechanical and electrical activity observed in regions yielding surface QSm waves. Depending upon their location and quantity, the patches of viable muscle persisting within the infarct undoubtedly influenced the appearance of the epicardial electrocardiogram. As previously shown, negative potentials prevail in all but a relatively thin epicardial layer of the normal ventricular wall. Presumably, therefore, surviving muscle at deeper intramural levels would contribute to the negativity of the surface QS wave; conversely, viable muscle in the superficial layers may account for the embryonic R wave and slurring of the QSm occasionally observed in the present series of experiments. Thus the coronary QS wave apparently sometimes results entirely from transmission of the negative cavity potential, as described by Wilson and confirmed in the present study, and sometimes represents a variable mixture of intramural

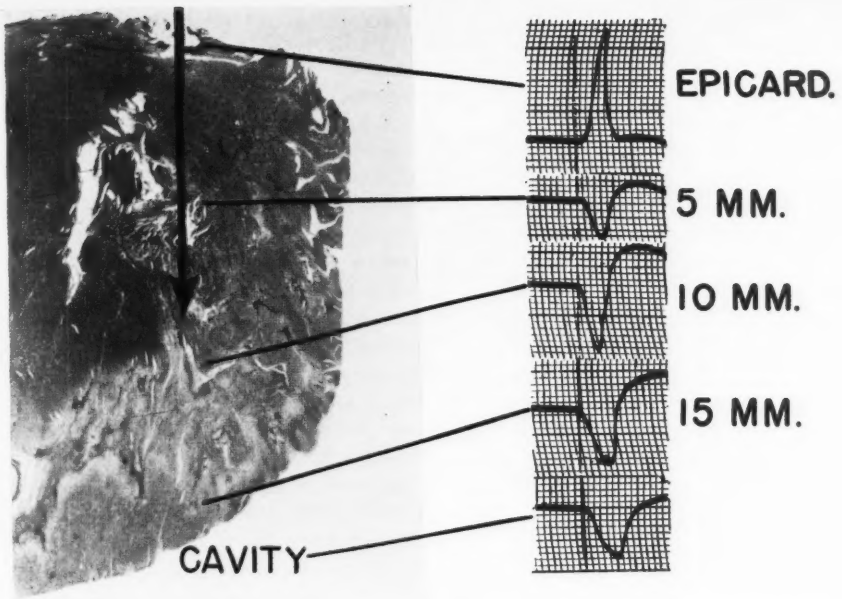

FIG. 4. Subendocardial infarct 26 days old. Magnification ×5.7. Arrow shows approximate location of plunge electrode. Mallory's connective tissue stain: blue, connective tissue; red, surviving muscle.

Contrary to prevailing theory, surface lead exhibits no QS deflection; only a large R wave is recorded. Current of injury obtained at 5, 10 and 15 mm. depths indicates presence of viable muscle.

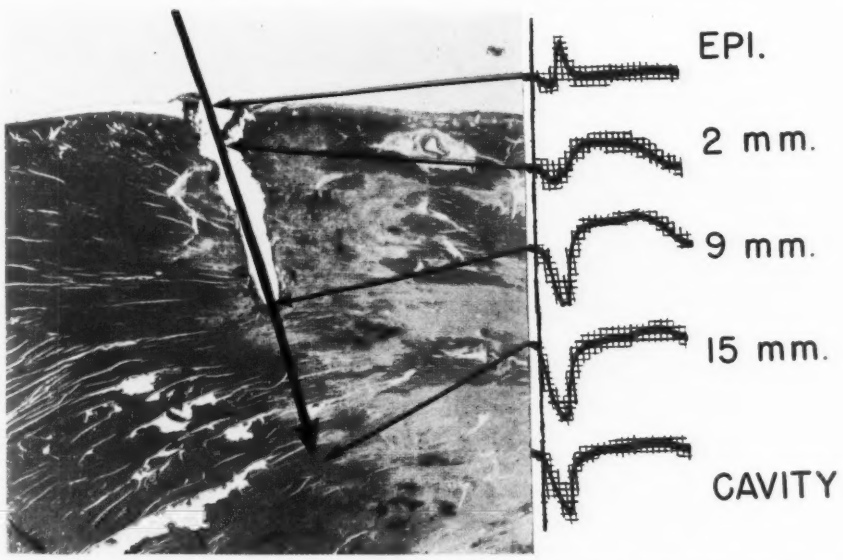

FIG. 5. Epicardial, intramural and cavity leads from margin of 27 day old infarct. Magnification ×7.8. Mallory's connective tissue stain. Arrow represents path of plunge electrode. Mostly surviving muscle to left; infarct to right. Hole extending to 9 mm. depth was made by plunge electrode.

Surface of margin exhibits minimal damage, yields small Q wave and relatively large R deflection. In tracings from various depths of the ventricular wall, the negative deflection is larger than in the surface lead, while the positive deflection disappears. These electrocardiographic findings indicate that the surface Q wave is not transmitted unaltered from the cavity, and the surface R wave is not transmitted from intramural muscle distant from the electrode.

(The use of color in figures 4 and 5 is made possible by a grant from Winthorp-Stearns, Inc., to the publication fund of the American Heart Association.)

and cavity potentials. If sufficient amounts of viable muscle remain within the deeper layers of an infarct, it is possible that the coronary QS wave may be derived solely from mural potentials. Such a circumstance was illustrated by the virtual disappearance of the positive deflection and the occurrence of a surface QS wave when the shell of positivity in the normal ventricular wall was experimentally destroyed.

Comment

In the present series of experiments, both the cavity and the mural types of surface QS wave frequently were recorded over different portions of the same infarct. In general, QSm waves occurred over a relatively large proportion of the surface of smaller infarcts, while QSc waves were more commonly obtained from larger infarcts. Although some large infarcts yielded only QSc waves, the majority included a zone of QSm waves over the periphery. Older lesions tended to present larger areas of QSc than of QSm waves, while the reverse was frequently true of more recent lesions. Thus the relative incidence of the two types of deflections appeared to be a function of the size and age of the infarct.

During the initial stages of the study, no distinction between cavity-type and mural-type QS waves was perceived upon inspection of epicardial tracings; this was true of leads recorded at 125 mm. per second as well as at normal paper speeds. After considerable experience had been gained, however, it was often possible to differentiate the two types of waves and, therefore, to predict the histologic findings by careful examination of the surface electrocardiogram. In the series of experiments now in progress, a "map" of each infarct is plotted purely on the basis of information gained from epicardial and intramural leads. With only occasional minor inaccuracies, the outlines of the infarct and the locations of viable muscle within its borders can thus be diagrammed before the histologic sections are made. Nevertheless, observers unfamiliar with the pertinent criteria seldom are able to differentiate QSc and QSm waves in epicardial leads. In precordial leads recorded on standard electrocardiographic equipment, the two types of QS waves usually are indistinguishable.

The Coronary QR Wave

According to current theory of the genesis of coronary QR waves, infarcted subendocardial muscle transmits the negative cavity potential to the epicardium, causing an initial downward deflection, after which overlying intact muscle contributes a positive potential, represented by the late R deflection.[11] Thus the surface or precordial QR wave is believed to occur over infarcts limited to the subendocardial region, as well as over the margins of transmural infarcts which have their greatest breadth in the subendocardium. Since recent investigations have yielded conflicting results concerning the histologic findings associated with QR waves,[12, 13] these deflections were considered an appropriate subject for experimental study.

Of the 41 instances of experimentally produced myocardial infarction in the present series, six presented histologic evidence of necrosis or fibrosis only at subendocardial levels. These six infarcts extended from the endocardium through one-eighth to one-half the thickness of the ventricular wall, in no instance destroying subepicardial or epicardial muscle. Standard limb leads and multiple precordial tracings were recorded from each animal several weeks after coronary ligation, the chest was reopened, and electrocardiograms were made directly from the epicardial surface over the lesion as well as from multiple intramural levels as previously described. Contrary to prevailing theory, both the precordial and epicardial depolarization complexes were normal, as shown by comparison with tracings from normal areas of the same heart and from other normal hearts; no QR waves were obtained. High-speed cinematographs recorded simultaneously with the direct leads in three instances likewise revealed no abnormality in the appearance or contractility of the epicardium overlying the infarct. Intramural tracings from various levels of the subendocardial lesion and overlying intact tissue appeared to be within normal limits in four of the six animals (fig. 4). In no instance did the intramural leads yield evidence supporting the

current theory of the genesis of coronary QR waves.

Since QR waves were not recorded over recent or chronic subendocardial infarcts, an experiment was performed to determine if such deflections might be obtained during the earlier stages of the lesion. In 18 animals, an attempt was made to produce acute myocardial necrosis by means of burns inflicted with an electric cautery. Histologic examination established that seven of these burns were purely subendocardial, extending from the cavity through one-eighth to three-fourths of the thickness of the ventricular wall. Immediate electrocardiographic exploration of the undamaged surface over the necrotic region consistently failed to reveal a negative initial deflection. In three animals, the R wave recorded over the burn was somewhat lower and later than in normal control leads, but nothing resembling a QR wave was seen. Similar observations have previously been made by Pruitt, Barnes and Essex.[14] Thus it appears that acute subendocardial necrosis produced by cauterization, like recent and chronic subendocardial infarction, does not necessarily produce coronary QR waves.

The consistent failure to obtain a negative deflection over pure subendocardial lesions, whether acute or chronic, suggests that some degree of epicardial damage is essential to the production of coronary QR waves. This conclusion is substantiated by findings in the 35 instances of transmural infarction produced during the study. In four such cases, QR waves appeared in both precordial and epicardial leads recorded over all or almost all portions of the lesion. Many of the remaining transmural infarcts presented QR deflections in precordial and epicardial leads from zones of variable width over the margins. Histologically, every region over which QR waves had been recorded was found to consist of a mixture of surviving muscle and fibrotic or necrotic tissue involving the epicardial surface (fig. 5).

Discussion and Clinical Applications

The present study of intramural, epicardial and precordial tracings in the experimental animal indicates that intramural depolarization potentials are not represented in leads facing the intact epicardium. This conclusion is derived from the following observations: (1) Although an overwhelming preponderance of intramural tissue in the normal heart is predominantly negative during ventricular depolarization, the depolarization wave in epicardial and precordial leads is normally positive. Burning or removal of the relatively thin shell of positive epicardial tissue diminishes the positivity of the surface depolarization potential

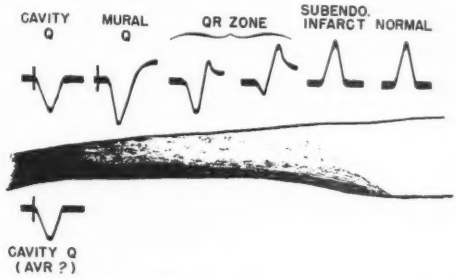

Fig. 6. Diagram showing relationship between electrocardiographic and histologic findings in region of myocardial infarction. From left to right: C-type QS wave, identical with cavity QS, is recorded over region of through and through infarction. M-type QS wave occurs over region containing mixture of surviving muscle and fibrotic tissue involving the surface; compared with the depolarization wave in simultaneous cavity lead, this mural type deflection often exhibits later onset, sharper downstroke and sharper tip. S-T segment elevation. QR waves are recorded from epicardial surface consisting of mixture of surviving muscle and infarcted tissue, but exhibiting somewhat less damage than the QS zone to the left. As the amount of epicardial damage decreases, the Q wave becomes smaller and the R wave larger. Normal surface tissue over regions of subendocardial infarction yields a normal depolarization wave. (Reprinted from J. Thoracic. Surg. **24**: 105, Aug., 1952.)

or actually changes the deflection from positive to negative. (2) If the epicardial zone of positivity remains intact, as in subendocardial infarction, the depolarization wave in precordial and surface leads remains positive. (3) If the epicardial region is damaged but contains a variable amount of surviving viable muscle, as in patchy transmural infarction, precordial and surface leads exhibit a negative deflection sometimes followed by a positive deflection. Preliminary correlations between electrocardio-

graphic and histologic findings in such lesions suggest that the degree of epicardial damage determines whether a QSm or QR wave is inscribed (fig. 6).

The preceding observations suggest that the status of underlying intramural muscle is not represented in epicardial and precordial electrocardiograms. Rather, it appears that such tracings merely provide a fair representation of epicardial potentials. Whether the deeper layers of ventricular muscle consist of completely fibrotic tissue, completely normal muscle, or a mixture of both, is not revealed by leads facing the epicardium. Consequently, prognostically unimportant epicardial disturbances may yield a greatly distorted electrocardiogram although the overwhelming mass of ventricular muscle remains normal. Conversely, severe pathologic changes within the depths of the ventricular wall may fail to reveal themselves in routine tracings if the epicardium remains intact. Finally, a coronary QS wave may signify either uniform through and through muscle death, or inactivity of only the epicardial zone of positivity, or any intermediate amount of myocardial damage. Such lesions can be reliably differentiated only by means of direct epicardial and intramural leads or by histologic examination. Unfortunately, the leads employed in clinical electrocardiography are comparatively remote from the heart and seldom provide sufficient information to determine the precise pathologic situation responsible for a given coronary QS wave.

An awareness of the limitations of clinical electrocardiography may serve to minimize certain diagnostic and therapeutic errors in patients with myocardial disease. All too commonly, individuals die of myocardial lesions which the electrocardiogram has failed to reveal. On the other hand, most internists have observed patients with greatly distorted tracings who nevertheless have small hearts, adequate myocardial function, and are able to lead active lives for years or decades; as noted by Wilson, these individuals frequently are advised to restrict or eliminate their normal activities, thereby contracting "coronary disease of electrocardiographic origin." Such apparent discrepancies between the electrocardiographic and clinical picture sometimes can be explained in terms of the concept that a "pure" QS wave may occur over regions containing significant amounts of viable muscle. The application of this concept to several common clinical situations is illustrated by the following examples.

Example 1. After experiencing a typical coronary occlusion, the patient exhibited QS waves in all precordial leads from V_1 to V_8 in the third, fourth and fifth intercostal spaces. A diagnosis of extensive myocardial infarction was made. Upon fluoroscopic examination, however, the heart appeared small and the left ventricle contracted well in each of numerous views; no regions of ballooning were observed. High-speed cinematographs of the fluoroscopic views confirmed the occurrence of systolic contractions in all visible portions of the left ventricle. Despite the ominous appearance of the electrocardiogram, the patient was in excellent condition. These cinematofluoroscopic and clinical findings indicate that the infarcted region contained enough viable muscle to maintain contractility. A similar situation was observed in experimentally produced infarcts which exhibited systolic contractions in regions yielding the mural type of QS wave.

Example 2. An 80 year old patient with a previously normal electrocardiogram experienced a massive gastrointestinal hemorrhage followed by shock. On the day following this episode, electrocardiographic studies showed QS waves in several precordial leads as well as in leads II, III and aV_F. Extensive anterior and posterior myocardial infarction was suspected despite the absence of pain or other evidence of coronary occlusion. After transfusions and other supportive treatment, the QS deflections gradually disappeared and were replaced by R waves. Several months later the bleeding recurred and a similar sequence of electrocardiographic events was observed: again, QS waves appeared and gradually were replaced by R waves. The transient occurrence of QS deflections on two occasions obviously could not have resulted from through-and-through death of cardiac muscle. A more reasonable interpretation of the findings is as follows: The patient presumably had coronary arteriosclerosis. When hypotension and shock followed hemorrhage, the blood flow to the entire heart became inadequate. The cells of the epicardial region were inactivated, so that the positive potential normally yielded by these cells was replaced by a negative potential transmitted from underlying regions. When the nourishment of the epicardium was improved by raising the blood pressure, the epicardial cells resumed their normal electrical activity, giving rise to an R wave. Hence the evanescent occurrence of QS waves may represent coronary insufficiency involving the epicardial region. This electrocardiographic phenomenon is not rare, even in the absence of shock.

Example 3. QS and/or QR deflections recorded over anterior infarcts often are replaced by R waves with the onset of a superimposed posterior infarction. Since the posterior lesion could weaken but not reverse the negative cavity potential, viable muscle within the anterior infarct must be responsible for the restoration of the precordial R wave. As hypothesized by Barker,[15] living tissue within the necrotic zone may produce positive voltages strong enough to obliterate QS and QR deflections when the posterior opposing forces are removed. Thus the QS wave originally recorded over the anterior infarct must be of the mural type.

Example 4. In patients with QS waves in all precordial leads, changes in the amplitude and direction of the T wave frequently occur either spontaneously after myocardial infarction or as a result of exercise or ischemia. Such variations in the T wave appear to be independent of variations in cavity potential and therefore may represent repolarization changes occurring in viable muscle within the infarcted ventricular wall. As demonstrated experimentally, T-wave changes could not be produced at the surface of infarcted regions containing only dead muscle, but were commonly observed over regions of patchy infarction which yielded mural-type QS deflections.

Example 5. In serial electrocardiograms recorded following coronary occlusion, QRS changes often do not occur until several weeks after the onset of S-T and T-wave abnormalities. The belated appearance of the coronary QS wave generally is unaccompanied by new clinical signs or symptoms, and the patient's condition may show uninterrupted improvement. In view of the clinical picture, it is improbable that the ventricular musculature depolarizes in an entirely normal manner for several weeks after occlusion, then suddenly develops a "hole" extending from endocardium to epicardium. A more logical explanation is that the deeper layers of the ventricle become electrically inactive without producing QRS alterations; only when prolonged ischemia finally causes muscle death or severe damage in the epicardial region is the normal R wave replaced by a coronary QS wave. This explanation is consistent with the observation that necrosis following coronary occlusion begins in the subendocardial region, which is farthest from the blood supply, and extends gradually toward the epicardial surface.[15] Thus the abrupt appearance of the QS waves without associated clinical changes presumably results from inactivation of the epicardial zone of positivity rather than sudden death of the entire thickness of the ventricular wall.

Summary

Experimentally produced myocardial infarction in 41 dogs has been studied by means of multiple precordial leads as well as direct leads from the epicardial surface, from several depths within the ventricular wall, and from the ventricular cavity. Intramural and cavity tracings were obtained with a specially designed "plunge" electrode. In 19 animals, high-speed cinematographs of the left ventricle were recorded simultaneously with epicardial leads. Finally, the electrocardiographic and cinematographic findings were correlated with histologic observations of the infarcted region.

Two types of QS deflections were recorded in direct leads from the surface of transmural infarcts. Electrocardiographic, cinematographic and histologic findings associated with the first type of surface QS wave established the absence of viable tissue in the subjacent myocardium and indicated that the negative surface potential was transmitted unaltered from the underlying cavity. The second type of surface QS wave was found only over infarcted regions containing islands of surviving muscle which at least partially determined the surface potential. Depending upon the amount of viable muscle present in the underlying region, the second type of QS wave was derived almost entirely from the cavity potential, entirely from intramural potentials, or from a variable mixture of cavity and intramural potentials. The first type of QS wave occurred most frequently over large, chronic infarcts, while the second type was more commonly observed over small lesions of recent origin and over the margins of larger infarcts. Several clinical cases illustrating the occurrence of QS waves over regions containing viable muscle are described.

Coronary QR waves were found only over regions of transmural infarction composed of a mixture of viable and necrotic or fibrotic tissue involving the epicardium. This pathologic picture was consistently present whether the QR deflection occurred over all portions of the infarct or only at the margins. Chronic subendocardial infarcts and acute lesions which did not involve the epicardial surface consistently failed to yield QR waves in precordial or epicardial leads.

The distribution of depolarization potentials in normal ventricles has been determined by means of multiple intramural and intraseptal leads. Approximately 80 per cent of the ventricular musculature exhibited predominantly negative depolarization potentials; positive po-

tentials prevailed only in a relatively thin epicardial layer of the ventricular wall and in the middle and right side of the septum. Burning or excision of the epicardial region of positivity drastically diminished the amplitude of the surface R wave or actually produced a surface QS wave. These findings, coupled with the consistent absence of QRS abnormalities in tracings recorded over infarcts not involving the epicardial region, are believed to indicate that leads facing the intact epicardium yield a fairly accurate representation of epicardial potentials and do not reflect the status of the large mass of underlying intramural muscle. The clinical implications of this conclusion are discussed.

Sumario Español

Por medio de pequeños electrodos intramurales en profundidades múltiples de la pared ventricular, potenciales fueron registrados en infartos del miocardio y en corazones normales. En 41 animales con oclusión coronaria, correlación electrocardiográfica e histológica indicó que las deflecciones QS coronarias pueden ser representadas por potenciales negativos trasmitidos desde músculo intramural viable como así de la cavidad. Deflecciones QR fueron obtenidas sobre infartos transmurales que contenían una mezcla de tejido viable y muerto, pero no sobre lesiones puramente subendocardiales. En el ventrículo normal, potenciales positivos de depolarización predominan grandemente sobre los potenciales negativos. Aplicaciones clínicas se discuten.

REFERENCES

[1] Drury, A. N., and Mackenzie, D. W.: The influence of vagal stimulation upon conduction through the branches of the A-V bundle in the dog. J. Physiol. **80:** 329, 1933.

[2] Bellet, S., and Johnston, C. G.: The effect of coronary occlusion upon the initial phase of the ventricular complex in precordial leads. J. Clin. Investigation **13:** 725, 1934.

[3] Scher, A. M., Paton, R. R., and Young, A. C.: Spread of electrical activity through the wall of the mammalian ventricle. Federation Proc. **2:** 139, 1952.

[4] Prinzmetal, M., Corday, E., Brill, I. C., Oblath, R. W., Kruger, H. E., Fields, J., Flieg, W., Goldman, A., Karpman, H., Kennamer, S. R., Osborne, J. A., Sellers, A. L., and Smith, L. A.: The Auricular Arrhythmias. Springfield, Ill., Charles C Thomas, 1952.

[5] Grishman, A., and Scherlis, L.: Spatial Vectorcardiography. Philadelphia, Saunders, 1952.

[6] Prinzmetal, M., Kennamer, S. R., Corday, E., Osborne, J. A., Fields, J., and Smith, L. A.: Accelerated Conduction: The Wolff-Parkinson-White Syndrome and Related Conditions. New York, Grune & Stratton, 1952.

[7] Sodi-Pallares, D., Rodrigues, M. I., Chait, L. C., and Zuckerman, R.: Activation of the interventricular septum. Am. Heart J. **41:** 569, 1951.

[8] Hecht, H. H., and Woodbury, L. A.: Excitation of human auricular muscle and the significance of the intrinsicoid deflection of the auricular electrocardiogram. Circulation **2:** 37, 1950.

[9] Wilson, F. N., Rosenbaum, F. F., and Johnston, F. D.: Interpretation of the Ventricular Complex of the Electrocardiogram. Advances in Internal Medicine, Vol. II. New York, Interscience Publishers, 1947.

[10] Prinzmetal, M., Schwartz, L. L., Corday, E., Sprintzler, R., Bergman, H. C., and Kruger, H. E.: Studies on the coronary circulation. VI. Loss of myocardial contractility after coronary artery occlusion. Ann. Int. Med. **31:** 429, 1949.

[11] Wilson, F. N., Johnston, F. D., Hill, I. G. W., and Grout, G.: The electrocardiogram in the later stages of myocardial infarction. Tr. A. Am. Phys. **48:** 154, 1933.

[12] Levine, H. D., and Ford, R. V.: Subendocardial infarction: report of six cases and critical survey of the literature. Circulation **1:** 246, 1950.

[13] Myers, G. B., Sears, C. H., and Hiratzka, T.: Correlation of electrocardiographic and pathologic findings in ring-like subendocardial infarction of the left ventricle. Am. J. M. Sc. **222:** 417, 1951.

[14] Pruitt, R. D., Barnes, A. R., and Essex, H. E.: Electrocardiographic changes associated with lesions in the deeper layers of the myocardium. Am. J. M. Sc. **210:** 100, 1945.

[15] Barker, J. M.: The Unipolar Electrocardiogram. New York, Appleton-Century-Crofts, 1952.

The Lewis A. Conner Memorial Lecture

The Nature of Cardiac and of Pulmonary Dyspnea

By DICKINSON W. RICHARDS, JR., M.D.

Dyspnea has many characteristics, differing from one clinical state to another. In pulmonary diseases the immediate cause is usually a disproportion between actual ventilation (breathing requirement) and breathing capacity. The hyperventilation of organic pulmonary disease is often mistakenly diagnosed as psychoneurosis. In early cardiac dyspnea, muscular fatigue associated with inadequate cardiac output may be a factor. True pulmonary congestion becomes important in more advanced left ventricular failure.

DR. Lewis Atterbury Conner, for whom this lectureship is named, died on Dec. 4, 1950, at the age of 84. A man of outstanding achievement and broad interests, he was throughout his long life primarily a clinician and a teacher of medicine. He was a master in the art and science of physical diagnosis, and was among those who hold firm to the belief that new advances should support and add to our simpler forms of knowledge, rather than replace them; that in the analysis and treatment of disease, laboratory findings, whatever their nature, should be our servants and not our masters.

In dealing with clinical situations generally one can well argue for an approach that is and remains comprehensive and inclusive, not exclusive or partial. As Whitehead[1] has so powerfully argued, the unit of reality is not a name, or a definition, or a formula, or even a theory. It is an event, a whole event, an experience. In clinical medicine the event is the patient.

Nowhere in medicine, perhaps, does the patient, whole and entire, so much need to be considered as in the field of respiration. Breathing is truly a strange phenomenon of life, caught midway between the conscious and the unconscious, and peculiarly sensitive to both.

Dyspnea, the major symptom of disordered breathing, which is the subject of this lecture, deserves, therefore, at the very start of our discussion, some orientation as to its intrinsic nature, and we come, even upon the most casual examination, to a realization that this is actually very different from one clinical state to another.

There is, for example, the dyspnea of the athlete, the mountain climber, a powerful muscular effort that becomes a part of the exhilaration of utmost physical effort. Very different is the dyspnea of asthma, the hard gasping, the combination of panic and exhaustion that oppresses the man whose airways are closing down; or the even more agonizing slow suffocation of the man with a tracheal tumor. Still different is the dyspnea of the cardiac, breathlessness compounded with profound exhaustion, sometimes also with cardiac pain, anxiety, and fear. Thus, in addition to differences in dyspnea itself, there are not infrequently adjuvant bodily disturbances, such as muscular fatigue or pain, that are unconsciously included, both by patient and doctor, in the symptom. In my further discussion, I shall endeavor to keep before us an awareness of these important distinctions.

Physiologically, dyspnea is defined as breath-

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ing associated with effort or distress, including here both subjective breathlessness and the objective evidences of labored breathing. As a simple description of the process, Cournand and I[2] suggested, a number of years ago, the statement that dyspnea occurs whenever the individual's actual ventilation cannot easily be provided by his breathing capacity—a statement not greatly different from that by Means[3] a decade earlier. This is obviously an oversimplification, but it applies well to several forms of dyspnea, especially those occurring in chronic pulmonary disease. It also brings forward three of the main features to be studied: breathing capacity, an anatomic and mechanical function; breathing effort, also a mechanical function; and ventilation or respiratory drive producing actual ventilation, largely a physicochemical or neurogenic function.

This simple statement of factors, or influences, producing dyspnea is set forth in the chart in figure 1, and this will form the plan of this presentation. Referring very briefly to

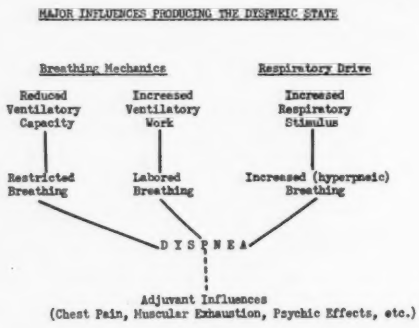

FIG. 1.

one or two basic methods of physiologic study, I will review a number of forms of clinical dyspnea, moving from the simple to the more complex. As certain types of pulmonary dyspnea are simplest, or seem to me to be so, I will discuss these first, and cardiac dyspnea last.

First as to the breathing capacity, or maximum breathing capacity itself. For many years the familiar vital capacity was considered to be an adequate measure of this function, but it became apparent after a time that this did not record speed of respiration and thus gave a poor correlation with ventilatory capacity in such conditions as obstructed or retarded breathing. The simplest method of including the time factor is to have the subject's maximum voluntary effort measured, as for example, by a tracing recorded on a moving drum to produce the familiar spirogram.[4] The details of the spirogram, in quiet and maximum breathing, and in normal and abnormal subjects, are well known and do not require special review.

The maximum breathing capacity has in fact been used as an index of pulmonary function or of dyspnea, just as vital capacity formerly was; and simplified indices have been developed which give a measure of speed and volume of ventilation. The recent air velocity index of Gaensler[5] is a modification of this, an extension of the earlier method of Gaubatz.[6] This, however, leaves out of consideration the amount that the individual actually does ventilate under the given conditions of rest or stress, whether hyper- or hypoventilation. There have also been indices of actual ventilation only, with no regard for ventilatory capacity. Among the best known of these is the so-called ventilatory equivalent of Anthony[7] and Knipping,[8] the amount of ventilation needed per liter of oxygen consumption, a factor obviously increasing as hyperventilation increases.

We have found, however, as might be expected, that ventilatory sufficiency, or insufficiency or dyspnea, is better evaluated by considering both factors, breathing capacity and actual ventilation. We have therefore used the *breathing reserve* (Knipping[9]), which is the maximum breathing capacity minus the actual ventilation, or the reserve of ventilation still available at any moment. This difference, expressed as a percentage of the maximum breathing capacity, was found by Cournand and myself[2] to define quite well the appearance of dyspnea, in various normal and abnormal subjects, when it reached a value below about 70 per cent or 65 per cent. Wright[10] has a somewhat similar dyspnea index which is the actual ventilation divided by the maximum breathing capacity. These two are of course only approximate measures of the entire process. The factors of rate of breathing and effort of breathing in the dyspneic state are not included. I will refer to these later.

The mechanical factors that may limit maximum breathing capacity are of course many: deformities of the chest cage, defects in the musculature involved in respiration, pleural thickening, hydrothorax, loss of pulmonary elasticity and expansibility through fibrosis or other intrinsic pulmonary disease, and other factors.

The many patients in this category can be illustrated by the first case, that of a woman of 40 with widespread fibrotic pulmonary tuberculosis, who had also had a partial left thoracoplasty. She became dyspneic on moderate exertion, the dyspnea subsiding promptly when she stopped and rested. Figure 2 shows a ventilatory tracing from each lung obtained by

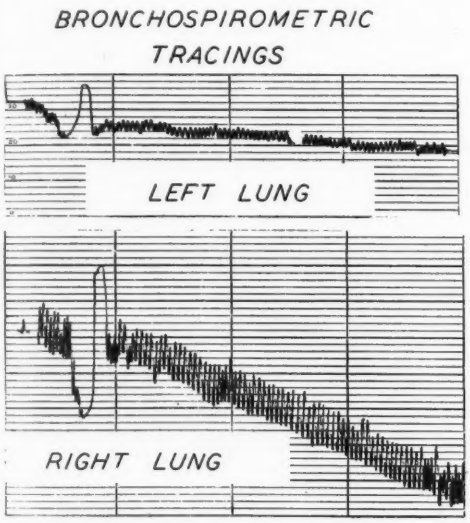

FIG. 2. Bronchospirometry. Patient A. S. Tracings indicate pulmonary ventilation, and oxygen consumption (upward slope of curve), from each lung.

bronchospirometry, and indicates a marked decrease in ventilatory capacity as well as oxygen consumption of the left lung. Table 1 gives her over-all respiratory function. As you will see, her difficulty is simply that of restricted breathing mechanics. Inelastic lungs have shrunk her vital capacity and reduced her maximum breathing capacity to one-half the estimated normal for an individual of her size and age. Her actual ventilation, in rest and exercise, and her blood aeration are practically within the limits of normal. She is dyspneic on exertion solely because of restricted ventilatory capacity.

This is probably the most benign form of dyspnea, at least in its moderate stages. With symptoms appearing only on considerable exertion, many are unaware of any limitation in their physical capacity. As Wright[11] has shown, many individuals with uncomplicated second-stage silicosis are in this category, so long as the silicosis is not complicated by emphysema.

In the majority of the more serious forms of diffuse pulmonary disease with functional disability, however, there is usually disturbance also in the third of the major influences on respiratory activity as given in our initial diagram, namely, respiratory drive or stimulus.

As to actual pulmonary ventilation, hyper- or hypoventilation in clinical conditions, there

TABLE 1.—*Chronic Pulmonary Tuberculosis*
(Patient A. S. Female, Age, 40 years)

	Observed	Normal Control
Vital capacity, cc.	1175	3480
Maximum breathing capacity, L./min.	52	97
Pulmonary ventilation, L./min./sq.m.B.S.		
Rest	3.4	3.2
After 1 minute exercise	13.1	11.9
Arterial oxygen saturation, per cent		
Rest	94	96
After 1 minute exercise	91	96

have been many general statements, but not much careful analysis. Even some modern textbooks, for example, still give out the general dictum that patients in chronic cardiac failure typically hyperventilate while patients with chronic pulmonary failure do not. We have been gathering data in both groups over a number of years, and can say categorically that no statement could be further from the truth than that.

But in order to understand the cause and nature of a patient's actual ventilatory performance, one should know several things: (1) the efficiency or inefficiency of the alveolar air exchange; (2) the effectiveness of aeration of the blood; (3) the effectiveness of transport of these gases, these chemical stimuli, to the respiratory centers by the circulation; and (4)

how these influences, and others as well, combine to produce the final respiratory stimulus.

1. The distribution of inhaled tidal air to perfused alveolar spaces may be somewhat unequal even in normal subjects, and is often markedly so in many forms of pulmonary disease. Some air spaces are greatly overventilated, others underventilated. There is ventilation of regions having no blood perfusion. In the terms of respiratory physiology, the ineffectual or dead space component of ventilation is usually increased in diffuse chronic pulmonary disease.[12] Thus to provide for adequate respiratory gas exchange total ventilation must also increase. Here respiratory rate is often of prime importance, the patient with rapid shallow breathing ventilating chiefly his pulmonary airways, with little effective aeration of alveolar spaces.

TABLE 2.—*Behavior of Arterial Chemical Agents in Various Types of Hyperpnea*

(from Gray, J. S. *Pulmonary Ventilation*)

Condition	Max. Vent. L./min.	Changes in Arterial		
		pO_2	pCO_2	pH
Anoxia	12	−	−	+
CO_2 Inhalation	70	+	+	−
Metabolic Acidosis	35	+	−	−
Moderate Exercise	50	±	±	±
Severe Exercise	120	±	−	−

2. As distribution of inhaled air deteriorates further, alveolar air stagnates in some parts, where active blood perfusion continues, and aeration of the blood becomes inadequate here, even in the presence of total pulmonary hyperventilation. Arterial anoxia then ensues. With a thickened or edematous alveolocapillary membrane, the tendency to anoxia is increased.[13]

The elimination of carbon dioxide by the lungs differs from that of oxygen in that with sufficient hyperventilation of perfused and well ventilated spaces, the stagnation in poorly ventilated spaces can often be compensated and blood carbon dioxide levels remain normal. When there is carbon dioxide retention in chronic pulmonary disease, this usually indicates an inadequate respiratory stimulus.[14] I will return to this point later.

3. If there is retarded blood flow, venous anoxia and hypercapnia are increased in the tissues, including the tissues of the respiratory centers, and this may increase the respiratory stimulus.

4. We have just remarked that with ineffectual alveolar ventilation, total ventilation "must be increased" to provide normal gas exchange. This teleologic statement, of course, explains nothing, and requires mechanistic support. How is such hyperventilation brought about? What are the active respiratory stimuli? This question brings us into the midst of a controversy that has been tossed about among physiologists for well over half a century. In his great book on *Blood: A Study in General Physiology*, published 24 years ago, L. J. Henderson[15] concluded that there was not one respiratory stimulus, but many. This point of view has been taken up again recently by J. S. Gray,[16] who has developed a number of quantitative relations, on the basis of published data. He demonstrates that low oxygen tension, or partial pressure, in the blood, high carbon dioxide tension, and increased blood acidity are all positive stimuli to the respiratory center. Depending upon the level of each in a given physiologic situation, these supplement or inhibit one another, and the net respiratory stimulus is the algebraic sum of all. Thus Gray finds that pure anoxia of marked degree is a powerful respiratory stimulus, but the usual hyperventilation in anoxia promptly lowers carbon dioxide partial pressure and raises pH and so the net effect is small. On the other hand, anoxia in the presence of normal or high carbon dioxide tension and low pH should cause, and does cause, very marked hyperventilation. Table 2, taken from Gray's monograph, shows how these three stimuli may interact in various clinical conditions associated with hyperpnea. In muscular exercise, the three stimuli are inadequate to explain total ventilation, and Gray postulates a fourth, as yet not identified.

Given a certain total respiratory stimulus, the actual manner in which ventilation is car-

ried out—rapid and shallow, slow and deep, regular or irregular—is conditioned, as Hess, Fleisch,[17] and others pointed out years ago, by the patient's anatomic limitations and by countless proprioceptive and other reflexes streaming in from all parts of the breathing mechanism. All breathing is thus reflexly stimulated and conditioned, just as all breathing is also chemically stimulated.

Finally, over and above the chemical and reflex influences, the final ventilatory performance is influenced, more or less, by conscious or subconscious psychic influences.

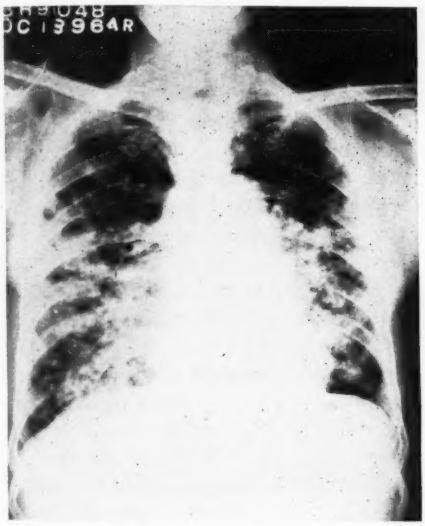

FIG. 3. Patient M. C. Advanced silicosis.

One further point on methods of study. To measure dyspnea, except in advanced states, the individual has to be put under some sort of stress. One simple technic has been the breath-holding time; but variations in conscious effort from patient to patient render this unreliable. The most direct and generally satisfactory is an exercise test. A continued mild-to-moderate exertion, such as walking on a treadmill, which provides a physiologic steady state, over several minutes' time, is best. As a simple index of pulmonary function, however, a single step test of brief duration is often adequate. In most of our clinical studies we have used a single step, 30 times in one minute, and measured ventilation at rest, during exercise, and for five minutes during recovery. This gives a fairly consistent increase in oxygen consumption, an index of the amount of additional work done, although the total "oxygen debt" may not be completely paid by the end of the five-minute recovery period.[13]

The next clinical case will illustrate the manner in which, in the course of severe, progressing pulmonary fibrosis, a restricted ventilatory capacity, combined with a hyperactive respiratory center, greatly aggravates the patient's clinical dyspnea. The patient was a man of 66 with advanced silicosis, complaining of severe dyspnea on mild exertion. Figure 3 shows the x-ray of his chest, and table 3 a summary of the findings on physiologic study. The patient has a moderately reduced vital capacity and maximum breathing capacity, but a striking thing also is his marked hyperventilation, both at rest and in the mild standard exercise (30 steps in one minute), ventilation being almost twice that of a normal subject. His dyspnea is easily explained, since the reduced breathing capacity and high actual ventilation leave him with a much reduced breathing reserve.

TABLE 3.—*Cardiopulmonary Function in Advanced Silicosis*
(Patient, M. C., Male Age, 66 years)

	Observed	Normal
Vital capacity, cc.	2210	3800
Maximum breathing capacity, L./min.	64	88
Ventilation, L./min./sq.m.B.S.		
Rest	5.1	3.9
1 minute exercise	23.0	11.2
1st minute recovery	22.0	14.5
Arterial oxygen saturation, per cent		
Rest	95	96
Exercise	97	96
Arterial CO_2 tension, mm.Hg		
Rest	34	40

But why should he hyperventilate? He has an increased pulmonary dead space—that is, he ventilates unperfused alveolar spaces—but

even so the ventilation of perfused alveolar spaces is such that he keeps his blood carbon dioxide level, his carbon dioxide tension, well below normal (34 mm. Hg compared with the normal 40 mm. Hg). Arterial oxygen saturation is normal, at rest and in exercise. There was no evidence of cardiac insufficiency here. Catheterization showed that cardiac output was normal; there was only a mild pulmonary arterial hypertension and no increase of systemic venous pressure.

Figure 4 shows the same phenomenon, a moderate hyperventilation compared with normal values in a group of 14 patients with uncomplicated pulmonary fibrosis, at rest, in exercise, and during five minutes' recovery.

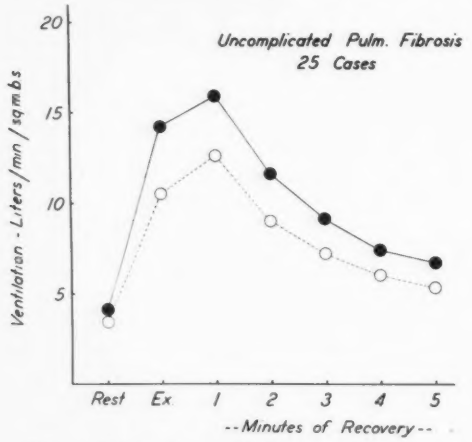

FIG. 4. Pulmonary ventilation, at rest, exercise, and recovery, in 25 cases of pulmonary fibrosis (solid line) compared with normal subjects (dotted line).

Is this hyperventilation functional, a sort of hysterical dyspnea? Such is always conceivable, but there is, by and large, nothing else to support such an explanation in this large group of chronic advanced cases of diffuse pulmonary fibrosis.

Is it reflex dyspnea? In the sense that the patient does overbreathe to the extent of keeping his blood carbon dioxide at an arterial tension of 34 mm. Hg, which is well below normal, one may well argue that the Hering-Breuer impulses or other reflex mechanism are exaggerated in this case. We do not have a complete and satisfactory explanation here, but there is some evidence to suggest that if we could add up correctly all the basic chemical stimuli, after the manner of Gray, we might come out with a sufficient chemical explanation. One fact of importance is that with lowered carbon dioxide tension, a respiratory center does become more sensitive. Another is that in this type of case, in spite of practically normal blood oxygen values and apparently normal circulatory performance, the administration of oxygen often definitely lowers pulmonary ventilation. This has been known for many years. It suggests that there may be here a significant anoxic respiratory stimulus, in spite of apparently normal arterial oxygen saturation.

But the question of the functional or psychic aspect of clinical dyspnea is a most important one, both in pulmonary and cardiac dyspnea, and frequently difficult of analysis. I am not speaking of the true respiratory neuroses; these are relatively simple, either the compulsion neurosis, the repeated sighing respirations, or the attacks of hysterical dyspnea in the typical anxiety state. The difficult problem is that of the patient with some pulmonary disease, and much dyspnea and hyperpnea.

An interesting group in this category is that studied during the war by Galdston, Luetscher, and their collaborators[18] following acute phosgene poisoning. These cases presented many interesting details; one of the striking features being the frequent persistence of the symptom of dyspnea long after the patient's x-ray had completely cleared, physical examination was normal, and pulmonary function measurements had returned nearly to normal, also.

I shall present one of their cases briefly: a woman of 43 with a past history including considerable nervous and emotional instability. She suffered moderately severe exposure to phosgene, with development of pulmonary edema and acute respiratory insufficiency, requiring pressure-oxygen therapy and other measures for several days. X-ray and physical signs then improved steadily, but for several months thereafter, her nervous symptoms were aggravated, and she suffered from exertional dyspnea and, in addition, from independent

episodes of breathlessness coming on without apparent cause.

The measurements of her pulmonary function several months after the phosgene exposure, when x-ray and physical signs were normal, consisted of a normal vital capacity, maximum breathing capacity that was somewhat reduced, some hyperventilation at rest and on exertion. Arterial oxygen saturation was essentially normal. Thus with the mild degree of these deviations from normal, it would seem that the functional factor here was an important one. On the other hand, the pattern of respiration was not dissimilar from that of the cases of unquestioned pulmonary fibrosis just considered. Are we entirely sure that this patient may not have had mild recurrences of pulmonary edema, giving symptoms, but subclinical to x-ray and physical signs?

There is no doubt that anxiety may play a part in the dyspnea of these patients, and the more so the more they become pulmonary cripples; and this mental state needs study and care. On the other hand, we are seeing more and more of these patients whose physical disease has been either undetected or else disregarded, and who are considered to be mental cases only. Surely there is no more bitter punishment that a doctor can inflict upon a patient than a mistaken diagnosis of psychoneurosis. With no treatment, understanding or even sympathy for his underlying condition, he is often driven, by doctor, friends, and family alike, into activities which he cannot endure. Physically sick and exhausted, he can get no honest hearing, his perplexity deepens into depression, only to have himself further stigmatized as a hopeless neurotic. Our pulmonary clinics are increasingly populated by the victims of these blunderings of our psychosomatic enthusiasts.

At all events, it would seem wise in cases like this *not* to brand the patient too freely as psychoneurotic; or at least to judge the special manifestations of neurosis on their own merits only; but in cases where there is or has been respiratory disease or injury, to treat the hyperventilation syndrome as primarily a response to organic disease.

A few comments now on dyspnea in the group of chronic pulmonary diseases known as diffusion insufficiencies. By diffusion insufficiency, I mean that group of diseases, to which Hamman and Rich[19] first called attention in this country, including beryllium granulomatosis, Boeck's sarcoid, scleroderma of the lung and other conditions in which the important pathologic lesion is the creation by the disease process of an alveolar-capillary block causing impaired diffusion of oxygen into the pulmonary blood. The symptoms are marked dyspnea, hyperpnea and tachycardia, cyanosis after exercise, cough, often febrile episodes, clubbing of fingers and toes. Hyperventilation is so marked

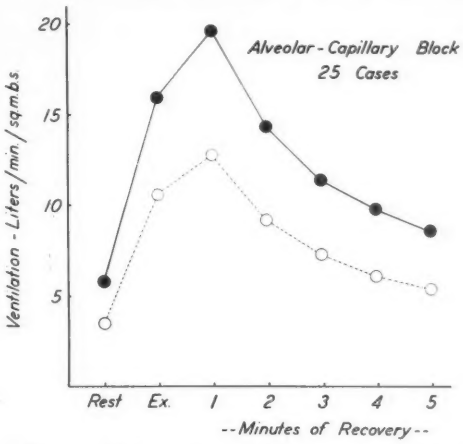

FIG. 5. Pulmonary ventilation in 25 cases of diffusion insufficiency (alveolar-capillary block), compared with normal subjects.

in these cases that they too have not infrequently been diagnosed as psychoneurosis.

Physiologically, these cases are characterized by a symmetric reduction in lung volumes due to their diffuse fibrosis, a remarkable maintenance of maximum breathing capacity, arterial oxygen saturation little reduced at rest but markedly decreased in exercise, carbon dioxide levels somewhat low in milder cases but essentially normal in the more advanced.[13]

The extent of their hyperventilation is shown in figure 5, and this sufficiently explains the urgent and continuous dyspnea which is the dominant symptom of this disease. On the Gray hypothesis, with a normal or nearly normal carbon dioxide pressure and an unimpeded anoxic stimulus, the chemical basis for hyperp-

nea is perhaps adequate but there may well be other factors. There is, for example, the question whether there may not be a cardiocirculatory element as well, a retarded circulation increasing the stimulus in the respiratory center. We have measured cardiac output in some of these cases and it appears to be adequate both in rest and in exercise, except late in the disease. A further evidence of the significance of anoxia in diffusion insufficiency is the striking relief which is obtained, with sharp reduction in ventilation, through adequate oxygen therapy.

I have given but little attention thus far to the second of the categories of ventilatory mechanics concerned in dyspnea, namely, the effort or work involved in the breathing process. Is the effort per breath increased in these cases of diffuse pulmonary fibrosis? We have no good information on this point. We do know that the air passages are not obstructed, but it may well be that the loss of elasticity in pulmonary tissues provides an added burden to respiratory effort. However this may be, this factor becomes a very potent contributing cause of dyspnea in the next and final group of pulmonary diseases to be considered, namely, pulmonary emphysema.

TABLE 4.—*Forms of Pulmonary Dysfunction Causing Dyspnea in Chronic Obstructive Emphysema*

I. Factors Decreasing Breathing Capacity, and Increasing Ventilatory Effort
Narrowing of Air Passages
Inelasticity of Pulmonary Tissue
Hyperinflation of Lungs and Chest
Spasm and Asynergy of Respiratory Muscles
II. Factors Increasing Respiratory Stimulus
Enlarged Intrapulmonary Volume, and Poor Distribution of Inhaled Air
Impaired Alveolar-Capillary Diffusion
Anoxia
Hypercapnia
Decreased Arterial pH

It would be difficult to construct, scarcely even to imagine, a type of disease in which there occurred simultaneously more different kinds of pulmonary dysfunction than are found in advanced pulmonary emphysema. Correspondingly, a great deal has been learned about pulmonary and cardiopulmonary function through continued studies, in a number of clinics in this country and abroad, on this disease or group of diseases.

Table 4 summarizes the more important of these dysfunctions. The basic change morphologically is usually a combination of obstruction of air passages, loss of intrinsic elasticity, and trophic change in pulmonary tissue. These lead early to the assumption of the chronically maintained state of hyperinflation of the chest, since thus air passages are wider, and intrapleural pressure can again be negative or neutral. But hyperinflation with elevated anterior chest and lowered diaphragm is most unfavorable for ventilatory activity. The whole muscular framework in emphysema becomes spastic and asynergic.[21] All these factors increase greatly the actual work or effort per breath. This was well demonstrated by Christie[20] some years ago in his measurements of intrapleural pressure, in relation to breathing, in normal and emphysematous subjects, in which he showed that inspiration and expiration in emphysema were associated with wide swings of pleural pressure above and below zero level, indicating an inelastic lung and greatly increased effort in providing its ventilation.

Intrapulmonary air exchange in emphysema is greatly compromised. Maximum breathing capacity is reduced, due chiefly to expiratory retardation. Hyperinflation, with increased residual air, means relative ineffectiveness of tidal air aerating the lung spaces, but much more important is the uneven distribution of mixing within the lung itself, some parts being hyperventilated, others greatly hypoventilated.[12, 22] The former leads to hyperpnea, the latter to anoxia and eventually to carbon dioxide retention. Finally, the attenuated pulmonary capillaries and often a progressively developing pulmonary arteriosclerosis lead to pulmonary arterial hypertension and eventually right heart failure.

Clinically, the progress of emphysema can be considered as falling into four classes.[22] At first there is decreased maximum breathing capacity, some hyperpnea, with therefore exertional dyspnea as a major symptom, but normal aeration of the blood. When pulmonary

ventilation deteriorates further, there is inadequate oxygenation of arterial blood, especially in exercise. Still further insufficiency brings inadequate carbon dioxide elimination by the lungs, and carbon dioxide levels in blood and tissues rise, along with more advanced anoxia. With the rising anoxia and carbon dioxide in rest and exercise of the four stages of emphysema are charted. Anoxia is of course now further increased, and the vicious cycle becomes in fact complete.

Thus in the most advanced emphysema, usually the cases with cor pulmonale in failure, the patients, while dyspneic, are sometimes

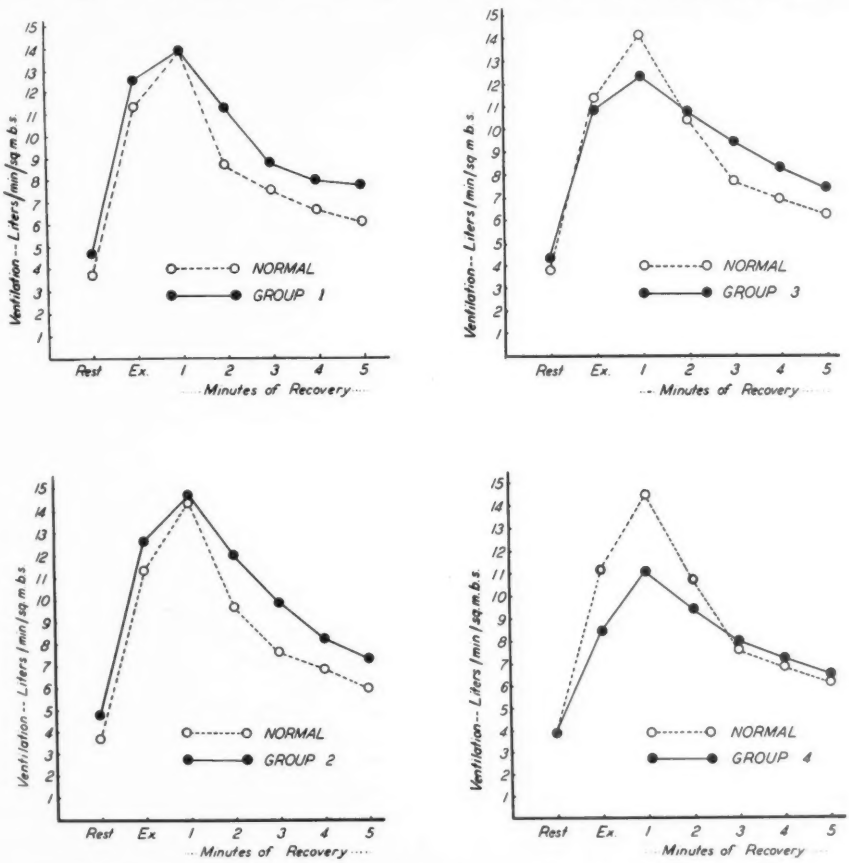

FIG. 6. Pulmonary ventilation in rest, exercise, and recovery in patients with advancing degrees of chronic pulmonary emphysema. (Reprinted from Medicine **28:** 201, 1949.)

levels, and falling blood pH, one would expect that the final stage would be associated with excessive hyperventilation and dyspnea, but at this point another change has occurred. The chronic hypercapnia, the increased carbon dioxide, actually deadens the respiratory center, and its insensitivity results in a failure of ventilatory volume even to reach normal values. This is shown in figure 6, where the ventilation not urgently so, in spite of profound anoxia. It is in this state that the use of morphine is especially hazardous, and oxygen therapy, by removing the anoxic stimulus to respiration, induces ventilatory stagnation, with excessive carbon dioxide retention and carbon dioxide narcosis.

With the above principles in mind, it is not surprising that the present-day treatment of

emphysema has shifted from the mere administration of cough mixtures, sedation and oxygen, to a vigorous effort to open the air passages, and ventilate the lungs by mechanical aids, corrective exercises, and artificial respirators.

To those of you primarily interested in heart disease, this excursion into pulmonary physiology has been a long introduction. But I believe that the nature of cardiac dyspnea can be clarified by comparison with these simpler pulmonary forms.

While the principles explaining the causes of dyspnea in heart failure have not changed greatly since, let us say, the publication of Harrison's *Failure of the Circulation* in 1935,[23] much has been added in the way of evidence: by cardiac catheterization, by new methods of pulmonary study, and quite recently by some of the physiologic results of mitral valve surgery.

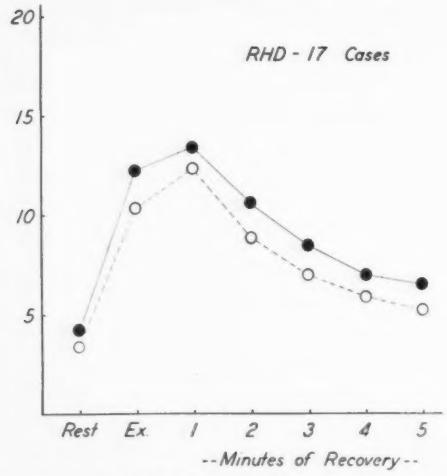

FIG. 7. Pulmonary ventilation in 17 cases of ambulatory rheumatic heart disease, with limited cardiac reserve.

Obviously the basic defect in heart failure as compared with pulmonary failure, is inadequate performance of heart and circulation, rather than inadequate performance of the lungs. Ever since it was known that the cardiac patient could not increase his oxygen consumption, his oxygen intake, in exercise as much as a normal subject, it was assumed that this was because cardiac output failed to increase adequately, oxygen thus could not be conveyed to tissues, and carbon dioxide from tissues, in sufficient quantity.[23] Relatively retarded blood flow, increasing anoxia and acidity in the respiratory center would induce hyperpnea; and the prolongation of the hyperpneic state during the recovery period, so characteristic a feature of cardiac dyspnea, was explained by the slow restoration of tissues to their metabolic resting state.

A more specific pulmonary component of congestive heart failure was postulated some 60 years ago by von Basch[24]—the stiffening of the lungs that would be expected to occur with pulmonary vascular congestion—and this received much emphasis when Peabody[25] demonstrated the decrease in vital capacity and ventilatory capacity with advanced congestive failure.

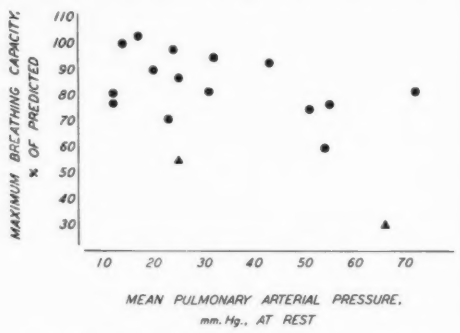

FIG. 8. Maximum breathing capacity and mean pulmonary arterial pressures at rest in 15 rheumatic cardiac patients (dots) and two patients with emphysema (triangles).

Cardiac catheterization studies have now amply confirmed both hypotheses: the failure of normal increase in cardiac output in exercise, and the early abnormal rise in pulmonary arterial pressures in exercising cardiac subjects.[26]

There has recently arisen also something of a controversy on the nature of cardiac failure, whether the failure of cardiac output is all-important, or whether the congestive state as such, "pressure failure," so to speak, may itself play a dominant part in the symptomatology.

Some evidence which I shall now present suggests that there may be differences in rela-

tive importance of these factors as one moves from the milder degrees of heart failure to the more severe. Specifically, the effects of retarded blood flow appear to be dominant early in failure, the evidences of pulmonary congestion becoming more important when failure is advanced.

Let us take first the ambulatory cardiac patient. West, Bliss, and Wood[27] have recently studied cardiopulmonary function in a group of subjects with rheumatic valvular disease, by measurements at rest and in steady exercise during cardiac catheterization.

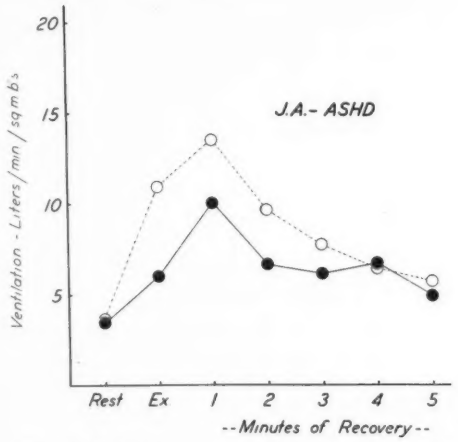

FIG. 9. Pulmonary ventilation of patient J. A. (see text).

Their performance was as follows: a moderate continued hyperventilation, a relatively poor increase in cardiac output in exercise, with a rise in pulmonary arterial pressure. Since there was some decrease in arterial carbon dioxide tension, a washing out of carbon dioxide by the hyperpnea, one could argue that some of the hyperventilation was on a "reflex" basis. So far as dyspnea is concerned, however, the actual increase in ventilation was slight, much less than in our pulmonary cases previously described. This is shown in figure 7. Furthermore, maximum breathing capacity was relatively well maintained, even with considerable increase in pulmonary arterial pressure. This is shown in figure 8. Thus breathing reserve was not greatly diminished.

Do we have then an adequate cause for the significant exertional symptoms that some of these patients complain of? It may be that there is increased effort per breath and that dyspnea may be aggravated by this. It seems probable, however, that there may be at least one other factor also.

A patient studied some years ago by Dr. Baldwin and myself may give a clue here. This was a man of 49 with longstanding cardiac hypertrophy and dilatation on a hypertensive basis. He had had one episode of congestive failure. At the time of study he was compensated at rest but his exercise tolerance was much reduced.

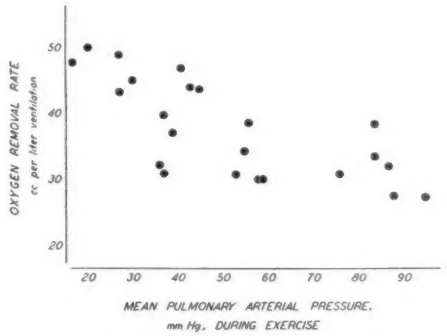

FIG. 10. Relation between oxygen removal rate (uptake) in cubic centimeters per liter ventilation, and pulmonary arterial pressure, in 23 observations in 20 rheumatic cardiac patients with diminished cardiac reserve.

In our study he endeavored to carry out a mild 30-step exercise test, but could not finish, stopping after 16 steps only. Examination of his pulmonary function showed that his vital and maximum breathing capacities were perfectly normal both before and after the test; there was no abnormality either in arterial oxygen saturation or in carbon dioxide. His pulmonary ventilation during the slight exertion was but little increased, actually significantly less than a normal subject with the 1-minute step test, as shown in figure. 9. Closer inquiry revealed that he really was not stopped because of dyspnea but because of fatigue or exhaustion. It was not cardiac pain; as a matter of fact, when the patient finally died two or three years later, he did not have significant coronary narrowing.

What was the cause of this muscular exhaustion? We have found it, as have others, to be a prominent symptom in some of our cases of advanced mitral disease admitted for surgery, and here it seems to be associated with very low and fixed cardiac output. These patients notice it more acutely if they suddenly become free of the symptom after successful commissurotomy. May it not be, therefore, that inadequate blood flow manifests itself by this symptom of fatigue, which has been mixed with, and yet is really separate from, the symptom of dyspnea itself? Perhaps by a more exact and careful clinical history, clinicians will be able to identify this fatigue or exhaustion factor, as well as by complex laboratory tests.

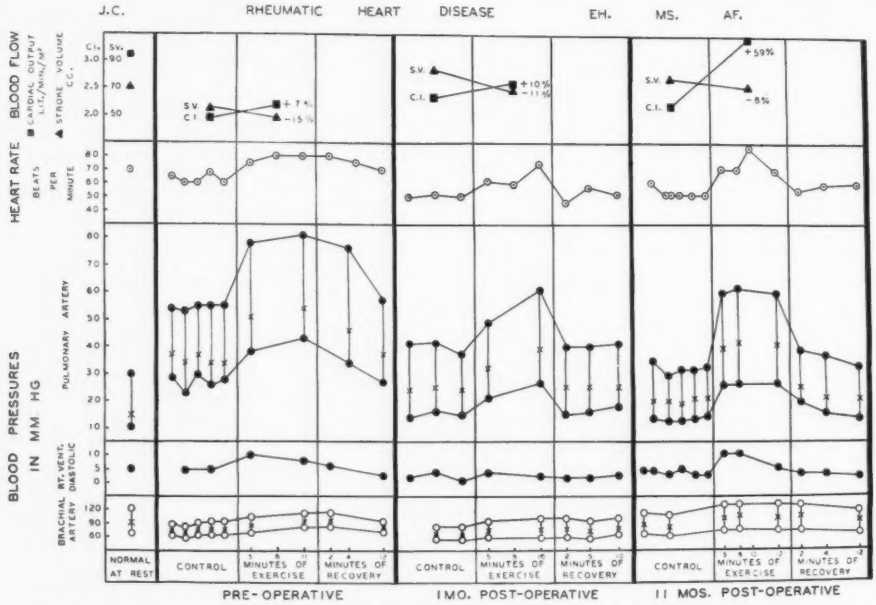

FIG. 11. Patient J. C. before and after mitral commissurotomy. Lower three graphs indicate intravascular and intracardiac pressures: pulmonary artery, end-diastolic in right ventricle, and brachial artery.

As the state of left ventricular failure advances, we find corresponding changes both in pulmonary and in cardiac measurements. Figure 10 from West, Bliss, and Wood[27] shows how the oxygen concentration in expired air, which is essentially the reciprocal of pulmonary ventilation, decreases with rising pulmonary congestive hypertension. Expired air oxygen concentration is used in these spot charts, in preference to actual volumes of pulmonary ventilation, since it indicates the degree of ventilation or hyperventilation per unit of oxygen absorbed, and therfore permits comparison of values in individual subjects with different oxygen intakes.

The relation with cardiac output in exercise is even more striking: there appears to be only a moderate increase in ventilation (decreased oxygen per cent) until cardiac output has dropped to a really low value, below which the degree of hyperpnea is markedly aggravated, presumably associated with hypoxia of brain and tissues. This is due in large part to retarded blood flow, though we are finding a fair number of cases in which the acute pulmonary congestion of exercise is associated with some arterial anoxia, with therefore a further anoxic respiratory stimulus. One wonders whether an abrupt shift of this kind, in pressure or output, or both, may not be the trigger that sets off an attack of paroxysmal dyspnea or cardiac asthma, this in turn induced by some small

change in vascular fluid balance, vasomotor state, or intercurrent infection, a small pulmonary embolus or other disturbance.

Effort of breathing is increased in pulmonary congestion. This was well shown in the original studies of Christie and Meakins.[28] By continuous intrapleural pressure recording, they showed markedly increased pressure swings between inspiration and expiration, during congestive failure, decreasing toward normal after recompensation.

As for the important question whether the pulmonary congestive state as such without alteration in cardiac output can be chiefly responsible for the disabling symptoms of advanced left heart failure, we believe that we have a definitive answer from some of our studies of mitral disease before and after commissurotomy. The following case is taken from a recent report[29]:

The patient, an electrician of 38, had had increasing exertional dyspnea, with attacks of paroxysmal dyspnea, for two years, and at the time of admission had been totally disabled for six months, was orthopneic, dyspneic on talking or the least exertion in the hospital. He had auricular fibrillation and mitral stenosis. Figure 11 shows his cardiodynamics pre- and postoperatively. You will see preoperatively a low cardiac output, which failed to increase on exercise, and a marked pulmonary hypertension, which rose further during and for a time following the exercise test.

In the next column of this figure are the measurements one month after a successful commissurotomy. The patient at this time was clinically well, with no dyspnea, no orthopnea, able to climb two flights of stairs, though his exercise tolerance was still significantly reduced. From the measurements you will see that while there was a slight increase in resting cardiac output, this did not increase further in exercise. The major change was the considerable drop in pulmonary vascular hypertension. The point here, therefore, is that pulmonary congestion would appear to be the chief and key disability in some at least of these cases of rheumatic heart disease in failure, and that its relief restores the patient to clinical compensation on limited activity.

The last column in figure 11 shows how 11 months later, this patient had made definite further improvement with even lower pulmonary vascular pressures and a better cardiac output. Now the patient had returned to normal activity in practically all respects.

The forms of dyspnea in far advanced congestive failure need not detain us long. Orthopnea, one of the standbys in differentiating cardiac from pulmonary dyspnea, seems at least partly explained since we know that the supine position brings more blood to the heart and lungs, adds to an already excessive cardiac filling, increases pulmonary congestion, decreases vital capacity and breathing capacity.

The increased tachypnea and hyperpnea in advanced heart failure raises again the question of reflex factors in lungs, great vessels or elsewhere, but again the marked and consistent relief obtained by oxygen therapy brings us back to a basic chemical control.

Cardiac asthma, sometimes truly asthmatic in form, is still basically an acute pulmonary congestion. While it may respond to bronchodilators, its relief more often depends upon the use of oxygen, frequently with positive pressure, upon digitalization, sedation, and diuretics.

Cheyne-Stokes respiration in heart failure has not been sufficiently explained. We know that it occurs clinically in advanced failure with retarded circulation, more in arteriosclerotic or cardiorenal forms than in rheumatic, that it never occurs in the dyspnea of chronic pulmonary disease. We can measure the anoxia and hypercapnia in the apneic phase and the hypocapnia in the hyperpneic; we can stop it by breathing carbon dioxide, occasionally by breathing oxygen. The exact chemical and dynamic circumstances that determine its onset, however, or the true relation between this and experimental periodic breathing of central nervous, or anoxic, or hypocapneic origin, are not known.

My last case and final point in this presentation concerns the patient bedeviled all his life by a cardiac murmur. It brings us back again to our starting point, the importance of considering the whole patient in the analysis of his clinical state. There is nothing new about

this. Dr. Conner's fine paper 20 years ago on the psychic factors in cardiac disorders[30] pointed the way. Various recent writers have referred to "iatrogenic" heart disease, an excellent term. We have encountered some flagrant examples, as others doubtless have also, in examining cases referred for cardiac surgery. They are individuals with a story of severe exertional dyspnea who have been found to have entirely normal cardiac and pulmonary function, both at rest and on the standard exercise test. Going back to the patient again, we have found that having had a cardiac murmur all his life, the patient has not been allowed exertion to the point of even normal breathlessness. He has suffered not from dyspnea, but the fear of dyspnea. Figure 12 shows the measurements on one such patient in rest and exercise. Perhaps as great satisfaction as we have had in our physiologic studies has been the demonstration to these patients that they need no severe restriction, but can lead essentially normal lives.

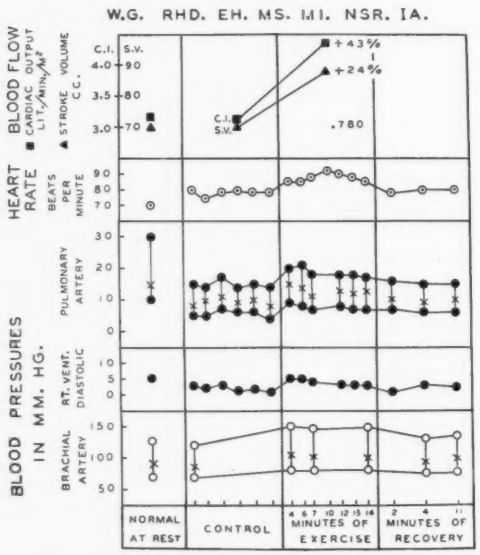

FIG. 12. Patient W. G. Dynamics of circulation.

It may seem inconsistent that I am arguing for more emphasis on the psychogenic factor in cardiac dyspnea, and less in pulmonary dyspnea. My impression may be mistaken, but it has been, in fact, that the diagnosis of neurosis is made rather too often in chronic pulmonary disease and perhaps not often enough in rheumatic heart disease with a valvular murmur but no failure.

In summary, I should like to stress the following:

1. Dyspnea, or distressed breathing, is a very different entity from one disease to another, and its special qualities in each deserve both physiologic and clinical analysis.

2. In general, it can be thought of as a balance between breathing capacity and breathing effort, on the one hand, and on the other, the actual ventilation produced by the existing respiratory stimulus.

3. The multiple or summation theory of respiratory stimulus has made a significant contribution to our understanding of dyspnea.

4. Hyperventilation is common both to pulmonary and to cardiac dyspnea, often more pronounced in the former.

5. One should be cautious in explaining dyspnea on a functional or neurotic basis when organic pulmonary disease is present.

6. In cardiac dyspnea, the factor of muscular exhaustion, due to reduced blood flow, may be significant.

7. Pulmonary hypertension and congestion may be the chief element producing symptoms in advanced left-sided congestive failure.

8. In general, the dyspnea of mild cardiac failure appears to be due chiefly to inadequate cardiac output; that of advanced congestive failure to pulmonary congestion.

9. "Iatrogenic" heart disease still occurs; that is, the patient with a cardiac murmur whose physical activity is needlessly restricted.

SUMARIO ESPAÑOL

Disnea tiene muchas características que difieren de un estado clínico a otro. En enfermedades pulmonares la causa inmediata es usualmente una desproporción entre la ventilación actual y la capacidad respiratoria. La hiperventilación de enfermedad pulmonar orgánica es frecuentemente confundida con psiconeurosis. En disnea cardíaca temprana, cansancio muscular con una producción total cardíaca insuficiente puede que sea un factor. Conges-

tión pulmonar es un factor importante en casos mas avanzados de decompensación del ventrículo izquierdo.

REFERENCES

[1] Whitehead, A. N.: Science and the Modern World. New York, Macmillan, 1925.

[2] Cournand, A., and Richards, D. W., Jr.: Pulmonary insufficiency. Discussion of a physiological classification and presentation of clinical tests. Am. Rev. Tuberc. **44:** 26, 1941.

[3] Means, J. H.: Dyspnea. Medicine **3:** 309, 1924.

[4] Hermannsen, J.: Untersuchungen ueber die maximale Ventilations-groesse (Atemgrenzwert). Ztschr. ges. exper. Med. **90:** 130, 1933.

[5] Gaensler, E. A.: Air velocity index, a numerical expression of the functionally effective portion of ventilation. Am. Rev. Tuberc. **62:** 17, 1950.

[6] Schmidt, W., and Gaubatz, E.: Spirometrische Funktionspruefungen von Herz und Kreislauf, in Kollapstherapie der Lungentuberkulose. Leipzig, Thieme, 1938.

[7] Anthony, A. J.: Funktionspruefung der Atmung. Leipzig, Barth, 1937.

[8] Knipping, H. W., and Moncrieff, A.: The ventilation equivalent for oxygen. Quart. J. Med. **1:** 17, 1932.

[9] —: Dyspnoe. Beitr. Klin. Tuberk. **82:** 133, 1933.

[10] Wright, G. W., and Filley, G. F.: Pulmonary fibrosis and respiratory function. Am. J. Med. **10:** 642, 1951.

[11] —: Industrial pulmonary diseases and capacity for work. Occup. Med. **2:** 546, 1946.

[12] Sonne, C.: Respiratory air exchange in the lungs under normal and pathological conditions. Acta med. scandinav., Suppl. **59:** 348, 1934.

[13] Baldwin, E. deF., Cournand, A., and Richards, D. W., Jr.: Pulmonary insufficiency. II. A study of 39 cases of pulmonary fibrosis. Medicine **28:** 1, 1949.

[14a] Meakins, J. C., and Davies, H. W.: Respiratory function in disease. London, 1925.

[14b] Scott, R. W.: Observations on the pathologic physiology of chronic pulmonary emphysema. Arch. Int. Med. **26:** 544, 1920.

[15] Henderson, L. J.: Blood: a Study in General Physiology. New Haven, Yale University Press, 1928.

[16] Gray, J. S.: Pulmonary Ventilation and Its Physiological Regulation. Springfield, Ill. Thomas, 1950.

[17] Hess, W. R.: Die Regulierung der Atmung. Leipzig, Thieme, 1931. Fleisch, A.: Neuere Ergebnisse ueber Methodik und proprioceptive Steuerung der Atmungsbewegungen. Ergebn. Physiol. **36:** 249, 1934. Christie, R. V.: Dyspnoea, a Review. Quart. J. Med. **7:** 422, 1938.

[18] Galdston, M., Luetscher, J. A., Jr., Longcope, W. T., and Ballich, N. L.: A study of the residual effects of phosgene poisoning in human subjects. I. After acute poisoning. J. Clin. Investigation **26:** 145, 1947.

[19] Hamman, L., and Rich, A. R.: Acute diffuse interstitial fibrosis of the lungs. Bull. Johns Hopkins Hosp. **74:** 177, 1944.

[20] Christie, R. V.: The elastic properties of the emphysematous lung and their clinical significance. J. Clin. Investigation **13:** 295, 1934.

[21] Cournand, A., Brock, H. J., Rappaport, I., and Richards, D. W., Jr.: Disturbance of action of respiratory muscles as a contributing cause of dyspnea. Arch. Int. Med. **57:** 1, 1936.

[22] Baldwin, E. deF., Cournand, A., and Richards, D. W., Jr.: Pulmonary insufficiency. III. A study of 122 cases of chronic pulmonary emphysema. Medicine **28:** 201, 1949.

[23] Harrison, T. R.: Failure of the Circulation. Baltimore, Williams & Wilkins, 1935.

[24] von Basch, S. S. K.: Die cardiale Dyspnoe und das cardiale Asthma. Klin. Zeit. und Streitsfragen, 1887. P. 82.

[25] Peabody, F. W.: Cardiac dyspnea. Harvey Lectures **12:** 248, 1916.

[26] Hickam, J. B., and Cargill, W. H.: The effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. J. Clin. Investigation **27:** 10, 1948.

[27] West, J. R., Bliss, H. A., and Wood, J. C.: To be published.

[28] Christie, R. V., and Meakins, J. C.: The intrapleural pressure in congestive heart failure and its clinical significance. J. Clin. Investigation **13:** 323, 1934.

[29] Richards, D. W., Jr., Harvey, R. M., Ferrer, M. I., West, J. R., Cathcart, R. T., and Cournand, A.: The influence of mitral valvular disease of rheumatic origin upon the dynamics of the circulation, with special reference to indications for surgery. First World Congress of Cardiology, 1950. Tome III, p. 190, Paris, 1952.

[30] Conner, L. A.: Psychic factors in cardiac disorders. J. A. M. A. **94:** 447, 1930.

The Selection and Medical Management of Patients with Mitral Stenosis Treated by Mitral Commissurotomy

By George C. Griffith, M.D., Harold Miller, M.D., Ph.D., Richard S. Cosby, M.D., David C. Levinson, M.D., Sim P. Dimitroff, M.D., Willard J. Zinn, M.D., Robert W. Oblath, M.D., Lawrence M. Herman, M.D., Varner J. Johns, Jr., M.D., B. W. Meyer, M.D., and John C. Jones, M.D.

The selection of patients for mitral commissurotomy must be made after considering all manifestations of the rheumatic state. A conservative approach is urged and no patients should be operated upon without evidences of increasing pulmonary hypertension and right heart strain. The preparation of the patient, the management of the arrhythmias during surgery and the postoperative care are the full responsibilities of the physician. A team composed of physiologists, cardiologists and surgeons must work together.

A NEW generation of dynamic surgeons and physiologists armed with experimental data gained through cardiac catheterization technics has approached the baffling hemodynamic problems of which mitral stenosis is an outstanding example. The clinical course of mitral stenosis in a fairly large group of individuals represents a slowly progressive sequence of events often leading to permanent cardiac disability. The development of auricular fibrillation and thromboembolism increase the likelihood of invalidism and result in an average life span of only 46 years, according to Levine.[3] This clinical pattern is physiologically defined in terms of elevated left atrial pressure behind the blocking action of the stenosed mitral valve. In order to establish a satisfactory pulmonary arterial gradient, elevation of pulmonary artery pressure must take place, with the vicious cycle ending in hypertrophy, dilatation and failure of the right ventricle. Therefore, the internist and cardiologist are compelled to evaluate the patients with mitral stenosis in order to submit to surgery that group of patients which can be helped most, to prevent needless surgery in that larger group which can be treated medically, and lastly, to find those patients in which surgery may be harmful. To do this successfully, the selection of cases depends upon many manifestations other than the narrowed mitral orifice. Table 1 serves a useful purpose in the evaluation of each prospective candidate for mitral commissurotomy. The historical background and review of the progress in this field are stated in recent excellent articles (Andrus[1] and Bland[2]) and will not be repeated here.

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Selection of Patients for Mitral Commissurotomy

1. The Natural History of the Disease. In acute rheumatic fever, active rheumatic carditis is present in 100 per cent of the cases, but it is not demonstrable in more than 50 to 60 per cent of the patients in the primary attack. It is very difficult to state when the rheumatic activity has subsided and become completely quiescent. There are many patients who never show evidence of demonstrable rheumatic activity, but who develop valvular disease later in life. Hall[4] demonstrated that 97 per cent of the patients with aortic valvular stenosis have evidence of active rheumatic carditis even though they have not had any evidence of active rheumatic fever during life. The absence of arthritis, chorea, fever, tachycardia, and even the absence of an increased sedimentation rate do not fully rule out a smoldering rheumatic state. As rheumatic fever is more com-

mon in the first three decades of life and tends to become quiescent in the third decade, there is much less danger of lighting up rheumatic activity in, or after, the third decade. For this reason patients over 25 years of age are more likely to be suitable for operative intervention than those under 20, as far as rheumatic activity is concerned. In our operated cases Aschoff nodules were found in 25 per cent of the amputated auricular appendages.

2. Multiple Valve Involvement. Aortic insufficiency is at present regarded as a contraindication, but many patients with mitral stenosis have a minimal early diastolic murmur audible along the left border of the sternum. This may be due to pulmonary incompetency, the so-called Graham-Steele murmur, resulting from pulmonary hypertension, and unless there is a Corrigan pulse and other peripheral signs of aortic regurgitation the early diastolic murmur alone should not contraindicate operation. Aortic stenosis, however, is a definite contraindication to surgery. Pulmonic insufficiency is not in itself a contraindication to mitral commis-

TABLE 1.—*Evaluation of Patients for Mitral Commissurotomy*

	Favorable	Less Favorable	Contraindicated
1. Age of patient	25 to 40 years	20 to 30 years	Over 45 to 50 years
2. Length of time of rheumatic fever	10 years	10 to 25 years	Over 25 years
3. Active rheumatic fever	Not present	Questionable presence	Positive presence
4. Mitral stenosis	Clinically "pure"	Impure	Impure
5. Mitral insufficiency	None	Minimal	Marked
6. Aortic stenosis	None	Minimal	Marked
7. Aortic insufficiency	None	Minimal	Marked
8. Mitral valve	Not calcified	Calcified	Markedly calcified
9. Left auricular enlargement	Definite, but minimal enlargement	Enlarged +2	(Giant) enlarged +4
10. Auricular fibrillation	Not present	Present	Uncontrolled
11. Pulmonary hypertension	Moderate or severe, twice normal pressure	Very high	Under twice normal or 2nd pulmonary art. dis. hemosiderosis, fibrosis
12. Subacute bacterial endocarditis	Absent	Absent	Present
13. Congestive failure	Absent	Controlled	Uncontrolled presence
14. Hemoptysis, paroxys. pulm. edema, intermittent rt. vent. failure	Absent	Present	Present
15. Thromboembolic phenomena	Absent	Previous presence	Uncontrolled presence
16. Incapacity	Increasing Class II to III	→ Increasing Class III ←	Class IV

surotomy. Organic tricuspid insufficiency leads to permanent liver damage and adds greatly to the risk.

3. Mitral Valve Insufficiency. This is without a doubt a most important factor since a high degree of mitral regurgitation is a grave threat to operative success and, at this time, is believed to be a definite contraindication to mitral commissurotomy. A loud, blowing systolic murmur in the mitral area associated with a large left ventricle and an increased atrial pulsation, as seen in the right oblique position, are important signs of mitral insufficiency. Free mitral regurgitation associated with some degree of mitral stenosis results in extreme enlargement of the left atrium. In relatively pure mitral

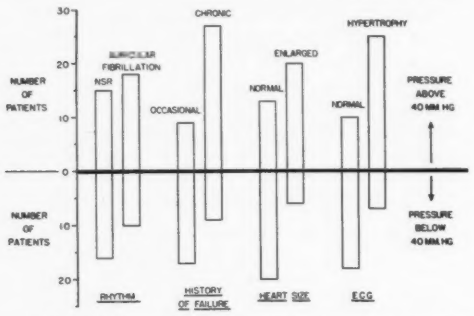

FIG. 1. The relation of mean pulmonary pressure to clinical data.

stenosis with minimal regurgitation, slight to moderate enlargement of the left atrium with hypertrophy of the muscle of the atrium is the rule. The massive left atrium usually indicates long continued rheumatic involvement of the muscle, a large degree of mitral insufficiency and associated auricular fibrillation. We accept the widely held view that evidence of mitral regurgitation of more than a minimal degree is a contraindication to mitral commissurotomy.

4. Calcification of the Mitral Valve. The mitral valve of many older patients shows some evidence of calcification which interferes with valvular function and makes surgery more difficult, especially in relation to the risk of thrombosis and embolization. Calcification of the mitral valve, if very marked, is a moderate contraindication but not an absolute contraindication at the present time, as the mitral commissures may be separated without much difficulty even though the anterior and posterior leaflets may be calcified. The danger is embolism from a calcific plaque.

5. Pulmonary Hypertension. The first effect of mitral stenosis is a rise of pressure in the left atrium and in the pulmonary vascular bed. Pulmonary artery pressure may rise to a high degree, even approaching the systemic arterial pressure. The degree of pulmonary hypertension is most difficult to evaluate clinically. It is best determined by cardiac catheterization. Mitral stenosis of severe degree occasionally has been found to be accompanied by a normal pulmonary artery pressure and in each case we learned later there was an active rheumatic carditis. Our best results have been obtained in those patients in whom operation has produced the most marked drop in the pulmonary artery pressure, as will be shown later. Therefore, it is important to know the pulmonary artery pressure, and if cardiac catheterization cannot be performed, then the following criteria are helpful.

(a) The mean pulmonary artery pressure has been compared with readily available clinical data (fig. 1). Using a mean pressure of 40 mm. Hg as the dividing line between high and moderately elevated pulmonary artery pressures, it is noted that normal sinus rhythm occurs equally in the groups with high and moderately high pressure. Auricular fibrillation occurs with greater frequency in those whose pressure is above 40 mm. Hg.

(b) Patients with a history of occasional failure are found to occur frequently in the group with moderately elevated pressure while patients with a history of chronic failure are found to belong almost wholly in the group with high pressure.

(c) A normal sized heart is found frequently in the group with moderately elevated pressure. Patients with enlarged hearts fall entirely in the group with high pressures.

(d) The same thing applies to patients who have normal electrocardiograms; that is, normal electrocardiograms are found much more frequently in those with a moderately elevated

pressure while electrocardiograms exhibiting evidence of right ventricular hypertrophy occur almost entirely in the group with high pressure.

If the clinician will use the readily available clinical data he may be able to avoid the necessity of cardiac catheterization as far as the selection of the patient for mitral commissurotomy is concerned. However, the benefits to be derived from mitral commissurotomy are determined best through the physiologic measurement of cardiac output and pulmonary artery pressures pre- and postoperatively (table 2).

6. Auricular Fibrillation. The presence of auricular fibrillation is not so much a contraindication to mitral commissurotomy as an indication that the optimum time for surgery may have passed. If auricular fibrillation has been present over a long period of time, it points to a proportionately greater dilatation than hypertrophy of the atrial muscle. However, if there is no congestive failure and the myocardium is relatively sound, controlled auricular fibrillation should not be a contraindication to mitral commissurotomy.

7. Right-sided Heart Failure. In patients with mitral stenosis, hemoptysis and pulmonary edema, evidence of right ventricular hypertrophy and intermittent right ventricular failure occurs. This is not a contraindication if the failure is controlled. It is good evidence of a severe degree of pulmonary hypertension. In this state mitral commissurotomy may give striking relief. In the late stages, however, where there is chronic, uncontrollable right ventricular failure with tricuspid insufficiency, increased venous pressure, engorgement of the liver, ascites and edema, mitral commissurotomy is definitely contraindicated. With respect to the myocardium in mitral stenosis, not all of the symptomatology is due to the mechanical effect of the obstruction, but some is due to the damaged heart muscle. Evidence of marked muscle damage is a contraindication to mitral commissurotomy. A damaged left ventricle may be unable to carry the increased load following the relief of the obstruction. It is important, therefore, to judge the optimum time when a mitral obstruction should be relieved, preferably before irreversible changes have occurred in the pulmonary vessels, in the right heart, and finally, in the myocardium.

8. Increasing Incapacity. The American Heart Association Classification of the functional capacity of the heart to perform work is most useful in the selection of patients as eligible candidates for mitral commissurotomy.[5] Since classes I and II represent organic disease with only slight limitation in work performance, these classes are ineligible. Class III represents a group of patients whose capacity to perform work is limited to the necessary movements of life. Therefore, it is most important to know if there has been a gradual reduction in the capacity to do work, that is, from class II to class III. On the other hand, many patients have gone beyond class III into class IV and are totally incapacitated, requiring bed rest and the entire medical armamentarium to maintain life. If patients in class IV can be fully compensated and for a short time returned to class III, surgery may be performed. The most important criterion is the estimation of the degree of incapacity in each patient.

TABLE 2.—*Relationship of Fall in Systolic Pulmonary Artery Pressure to Clinical Result*

1. E. Y.	60	Chronic heart failure to normal activity
2. L. M.	45	
3. M. C.	29	
4. J. L.	18	Some improvement in cardiac reserve
5. C. F.	11	
6. H. H.	7	Questionable or no improvement
7. R. H.	3	
8. M. S.	0	

9. Thromboembolism. Thromboembolism is a strong indication to perform mitral commissurotomy. If there is a recent history of major or minor arterial or venous embolism and the patient has recovered, there is good reason to lessen the stasis in the left atrium. The improvement in cardiac output likewise lessens the danger of venous thromboembolism. The amputation of the left auricular appendage plus the decrease in pooling in the left atrium is one of the great advantages resulting from mitral commissurotomy.

Management of Patients Selected for Mitral Commissurotomy

This is the task of the internist and cardiologist. The nutrition and state of well-being of each candidate should reach its maximum level. Patients with incapacity to perform normal functions, willingly accept the possible advantages of surgery. The cardiologist, therefore, must plan a program so that auricular fibrillation and congestive failure are controlled. This requires digitalization to keep the ventricular rate between 70 and 80 and a diet to eliminate an excess of salt and water, with a high protein intake to improve the liver function. This objective can be attained by a diet composed of protein, 1.5 Gm., carbohydrate, 2 Gm. and fat, 1 Gm. per kilogram of body weight with not more than 2 Gm. of sodium chloride per day. Distilled water, ad libitum, is used. Mercurial diuretics are used with care to promote diuresis, but never dehydration, because of the increased danger of thrombosis during the dehydrated state. If congestive failure cannot be controlled on this regimen, then a liquid diet made up from Lonalac, 250 Gm., Protenum, 100 Gm., cane sugar, 125 Gm., in 2000 cc. of distilled water plus 500 cc. of pure orange juice is given throughout the 24 hours. This formula has been found adequate to improve the liver function while compensation is being restored.

The patient should not be submitted to surgery if there is evidence of congestive failure, liver engorgement or myocardial irritability other than the auricular fibrillation. Preoperative medication other than that used to control the heart rate and the congestive failure should be minimal. We have found that 50 to 75 mg. of Demerol is sufficient.

The cardiologist must observe the patient during anesthesia and through surgery; direct-writer electrocardiographic recording and blood pressure determination are requisite. The team composed of the anesthetist, surgeon and cardiologist must work closely together. It is in this manner that any alteration of the hemodynamics of the surgical patient is quickly detected and the cause determined. If the heart rate slows dangerously, atropine or isopropyl norepinephrine, given intravenously, is indicated. When the blood pressure drops and there is electrocardiographic evidence of coronary insufficiency, a vasopressor drug such as methoxamine in a 5 mg. intravenous dose is indicated. If rapid auricular fibrillation occurs, ouabain is given slowly intravenously while the surgeon waits until control is gained. When ventricular irritability develops the surgeon waits, and if the irritability does not subside promptly, then intravenous procaine amide in a dosage of 500 to 1000 mg. is given. In other words, the surgeon is free to concentrate on his work while the anesthetist maintains the lightest possible anesthesia with full oxygenation, and the cardiologist is responsible for the function of the heart at all times. Blood or plasma are infused as needed to prevent shock.

Postoperatively the cardiologist continues full responsibility for the physiologic state of the heart. Hydration must be maintained to prevent fever, tachycardia and thromboembolism. The preoperative diet and digitalis are reinstituted within 12 to 24 hours. The head of the bed is elevated moderately as soon as full consciousness is restored. Deep breathing and arm and leg movements are insisted upon at an early time and the patient is gotten out of bed on the commode within four to six days. An x-ray film of the chest and an electrocardiogram are made prior to discharge from the hospital. The average hospital stay is five days preoperatively and 10 days postoperatively. At home, if there has been no sign of failure, the patient rests in bed with bathroom and dining-room privileges for 10 days and then gradually increases physical activity.

Postoperative Depo-Heparin, 200 mg. plain, intramuscularly, every 18 hours, is started within six hours and continued for three to four days if thrombi have been found in the atrium. Attempts to convert auricular fibrillation to sinus rhythm are not made until one or two months have passed.

Results

Of the first 35 patients on whom mitral commissurotomies were attempted, eight were lost. None has been lost in the last 39 operations. It is believed that a lowered mortality rate can be obtained by careful selection, pre-

operative preparation, team work among the cardiologist, anesthetist and surgeon during surgery, and wisely directed postoperative care.

Mitral commissurotomy was performed in 74 patients prior to May 15, 1952. Of this number, preoperative cardiac catheterizations have been done in 31 and postoperative catheterizations have been done in eight. A short term clinical evaluation of 2 to 24 months has been made. The evaluation is not the opinion of one man, but of the team composed of the cardiologist, physiologist and surgeon, who meet once each week. On the basis of the combined opinion, the following estimation has been made. About one-third of the 74 patients has been greatly improved. The patients feel so much better that they tend to disregard the physician's instructions and advice. About one-third is markedly improved, the team believes, and the patients again feel greatly improved. The remaining one-third shows little or no evidence of change in the murmurs or in the physiologic function of the heart, and has been long in recovering from the surgery. None has been made worse except that mild reactivation of rheumatic fever has occurred in two cases. Eight deaths have occurred.

TABLE 3.—*Causes of Eight Deaths in 74 Patients on Whom Mitral Commissurotomy Was Performed*

Cardiac Arrest	2
1 During Anesthesia	
1 During Surgery	
Ventricular Fibrillation	1
Embolic Phenomena During Surgery	2
1 Calcified Plaque	
1 Thrombus	
Ruptured Valve with Acute Congestive Failure	1
Ruptured Left Atrium	1
Cerebral Thrombosis (Late)	1

TABLE 4.—*Complications During Surgery*

1. Cardiac Standstill
2. Cardiac Arrhythmias
   a. Auricular Premature Beats
   b. Supraventricular Tachycardia
   c. Nodal Rhythm
   d. Ventricular Premature Beats
   e. Bigeminal Rhythm
   f. Ventricular Tachycardia
   g. Ventricular Fibrillation
3. Hypotension
4. Hemorrhage
5. Thromboembolic Phenomena
6. Rupture of Left Auricle

Cardiac arrest during surgery is a real problem which must be dealt with promptly by both pharmacologic and surgical means (table 3). Many patients develop arrhythmias, but it has been learned that if the finger is removed from the valve area and held in the lumen of the atrium, the arrhythmias tend to disappear promptly (table 4). Embolic phenomena represent a real threat to the success of the operation. At least one-half of our patients have had thrombi in the left atrium. Thrombi which become detached are permitted to flow out through the opened auricular appendage. Occasionally a small embolus passes through the mitral valve. A calcified plaque on one occasion became dislodged from the mitral valve and passed to the middle cerebral artery, causing paralysis and death promptly. One case of acute congestive heart failure occurred because the valve leaflet was ruptured, resulting in acute mitral insufficiency. Another patient died from a rupture of the left atrium. This was not the fault of the surgeon, but of the cardiologist who sent this patient with a giant left atrium to the surgeon. When dehydration occurs postoperatively, especially in those patients with hypotension, cerebral thrombosis is a real danger. One such case has been lost.

TABLE 5.—*Postoperative Complications in 74 Patients on Whom Mitral Commissurotomy was Performed*

1. Reactivation of Rheumatic Fever	2
2. Hemiplegia, Transient	1
3. Chest Pain (Parietal)	1
4. A.V. Nodal Rhythm (New)	1
5. Auricular Fibrillation (New)	1
6. Congestive Failure (Recovered)	1
7. Cardiac Enlargement	3
(Temporary)	1
8. Mitral Insufficiency (Excessive)	3

The complications which the cardiologist must face during surgery are related above. Under the heading "Management" we have mentioned the use of atropine and isopropyl norepinephrine for the treatment of bradycardia and cardiac standstill. The atrial arrhythmias are best treated with a quick-acting digitalis or digitalis-like preparation such as

ouabain (table 4). The ventricular arrhythmias are best controlled with procaine amide, 500 to 1000 mg. intravenously. Hypotension is treated by the use of methoxamine compounds such as Vasoxyl or Wyamine. Hemorrhage is treated by replacement therapy. Thromboembolic phenomena are treated best by using the anticoagulants prior to surgery in those patients who have had recent emboli. The anticoagulant is stopped preoperatively for 24 to 36 hours and reinstituted, using Depo-Heparin, six hours after surgery. The complications following surgery are enumerated (table 5). These are treated by the clinician in the accepted manner, that is, by bed rest, digitalization, dietary management and mercurial diuretics.

Summary

To evaluate a patient with mitral stenosis all the manifestations of the rheumatic state must be considered. Only those patients with a narrowed mitral orifice whose capacity to perform work has been diminished are considered eligible for surgery. The criteria whereby selection is made are enumerated. The management of the patient before, during and after surgery is a team job, with the internist or cardiologist carrying the main responsibility.

Addendum

Since this study was reported, 52 additional patients have been operated upon, one patient being lost through uncontrolled ventricular tachycardia. This result has been accomplished by strict adherence to the criteria for the selection of and management of patients for mitral commissurotomy which have been outlined in this paper.

Acknowledgments

We wish to acknowledge our indebtedness to Miss Mary Mayo and Dr. Andrew Farr for valuable technical assistance.

Sumario Español

La selección de pacientes para comisurotomía mitral se debe hacer considerando todas las manifestaciones del estado reumático. Un acercamiento conservativo se urge y ningún paciente se debe operar a menos que no haya evidencia de aumento en hipertensión pulmonar y esfuerzo del corazón derecho. La preparación del paciente, el tratamiento de las arritmias durante la operación y el cuidado postoperatorio son responsabilidades del médico internista. Una cooperativa de fisiólogo, cardiólogo y cirujano deben funcionar juntos.

REFERENCES

[1] Andrus, E. Cowles: The surgical treatment of mitral stenosis. Ann. Int. Med. **35:** 476, 1951.

[2] Bland, Edward F.: Surgery of mitral stenosis, Circulation **3:** 290, 1952.

[3] Levine, S. A.: Clinical Heart Disease, ed. 3. Philadelphia, Saunders, 1945. P. 42.

[4] Hall, E. M., and Tsutayo, Ichioka: Etiology of calcified nodular aortic stenosis. Am. J. Path. **16:** 761, 1940.

[5] Harken, Dwight E., Ellis, L. B., Dexter, Lewis, Farrand, R. E., and Dickson III, J. F.: The responsibility of the physician in the selection of patients with mitral stenosis for surgical treatment. Circulation **5:** 349, 1952.

Prevention of Plasma Cholesterol Elevation and Atheromatosis in the Cholesterol-Fed Bird by the Administration of Dihydrocholesterol

By M. D. Siperstein, M.D., C. W. Nichols, Jr., M.A., and I. L. Chaikoff, M.D.

The effect of the addition of dihydrocholesterol to a high cholesterol diet has been studied in the chicken. It is shown that in this species the elevated plasma cholesterol and resulting atherosclerosis can be reduced to normal levels by such a procedure.

ACCORDING to present concepts, the level of plasma cholesterol or some component thereof, is a critical factor in the development of arteriosclerosis. It is not surprising, therefore, that, as a means of preventing arteriosclerosis, attention has been focused upon methods for lowering the level of circulating cholesterol. Until recently the feeding of a diet low in lipids has been the only method proposed for achieving this aim. But it is apparent that the control of diet is difficult, if not impractical, for the population as a whole.

In this laboratory we have approached this problem from a different point of view, namely, we have sought methods that will maintain a normal cholesterol level in the plasma even in the presence of a high cholesterol intake. Our first attempt to prevent the rise in plasma cholesterol in cholesterol-fed chickens was by the feeding of ferric chloride.[1] Although the administration of this salt kept the level of plasma cholesterol from rising excessively, the prolonged feeding of large amounts of iron, as was to be expected, proved noxious.* This experiment did, however, show the feasability of such an approach to the control of the level of plasma cholesterol.

The recent demonstration by Peterson, that mixed soybean sterols prevented the rise of plasma cholesterol[2] and reduced the incidence of atherosclerosis[3] in birds fed cholesterol, then led us to investigate the possible blocking action of animal sterols closely related to cholesterol. Dihydrocholesterol† was first chosen for study because of its close structural similarity to cholesterol—it differs only in the saturation of the double bond between carbons 5 and 6. It is shown here that the administration of dihydrocholesterol to birds fed a diet containing 1 per cent cholesterol almost completely prevented both the rise in plasma cholesterol and the ensuing atherosclerosis.

Experimental

Twenty-two White Leghorn cockerels, obtained at the age of 3 months from the Department of Poultry Husbandry, were fed Purina Broiler Chow (starter ration) for two weeks. At the end of that time a blood sample was taken for determination of the basal plasma lipids. The birds were then divided into three groups and fed the diets shown in table 1. These diets were fed *ad libitum* for 11 weeks. The average daily food consumption for each group is likewise shown in table 1, and their growth is shown in figure 1. During these 11 weeks, five blood samples were drawn from each chicken. Total plasma cholesterol was determined by a modification of the method of

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* In these initial experiments we used a diet containing 3 per cent ferric chloride. Experiments with smaller doses, presumably nontoxic, are underway.

† We are indebted to Dr. R. E. Waterman of the Schering Corporation for generously supplying the dihydrocholesterol used in this study.

TABLE 1.—*Composition of Diets and Food Consumption*

Group number		1	2	3
Composition of Diets All diets consisted of Purina Broiler Chow (starter ration) to which was added one or more of the following constituents:	Wesson Oil	5%	5%	5%
	Cholesterol	None	1%	1%
	Dihydrocholesterol	None	None	2%
Group symbol in Figures 1 to 4		○	△	□
		Gm.	*Gm.*	*Gm.*
Food Consumption Each value represents the average amount (Gm.) consumed per bird per day.	1st week	—	70	73
	2nd week	81	70	76
	3rd week	90	72	79
	4th week	82	76	89
	5th week	79	74	84
	6th week	88	84	89
	7th week	83	88	90
	8th week	73	88	85
	9th week	81	82	92
	10th week	105	81	91
	11th week	92	76	84
	Average	85	78	85

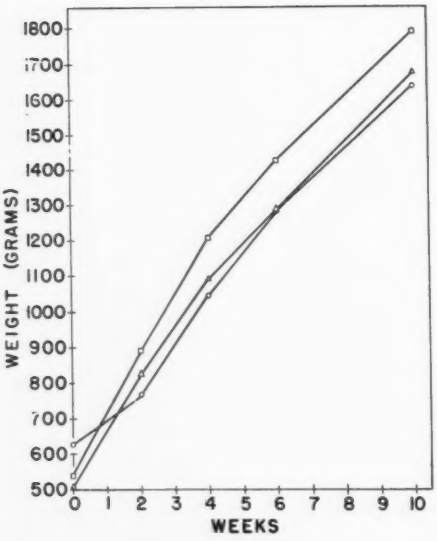

FIG. 1. Growth curves for the three experimental groups.

○—Birds fed basal diet.

△—Birds fed basal diet to which was added 1 per cent cholesterol.

□—Birds fed basal diet to which were added 1 per cent cholesterol and 2 per cent dihydrocholesterol.

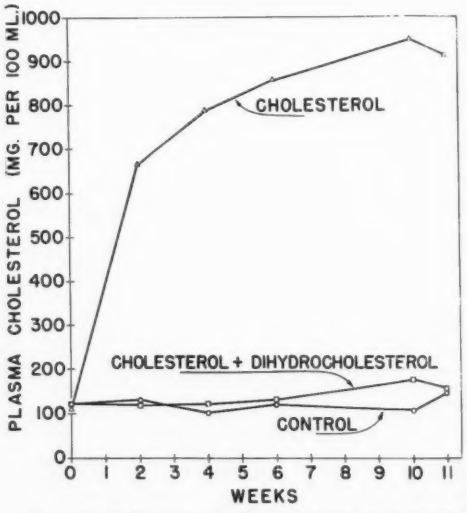

FIG. 2. Influence of dihydrocholesterol feeding upon plasma cholesterol levels of the cholesterol-fed chicken.

○—Average plasma cholesterol levels of eight birds fed a basal diet (Purina Broiler Chow plus 5 per cent Wesson Oil).

△—Average plasma cholesterol levels of eight birds fed a basal diet plus 1 per cent cholesterol.

□—Average plasma cholesterol levels of six birds fed a basal diet plus 1 per cent cholesterol plus 2 per cent dihydrocholesterol.

Sackett,[4] phospholipids by the method of King[5] and fatty acids by the method of Bauer and Hirsch.[6]

The plasma levels of cholesterol and phospholipids remained relatively constant in the control birds (figs. 2 and 3), while the fatty acid values in this group (fig. 4) decreased during the course of the study. The chickens receiving 1 per cent cholesterol in their diet manifested the usual pronounced rise in plasma cholesterol, phospholipids, and fatty acids (figs. 2, 3, and 4). Thus by the end of the second week, the average plasma cholesterol value was 665 mg. per 100 ml., by the end of the sixth week, 855 mg. per 100 ml., and 948 mg. per 100 ml. by the end of the tenth week.

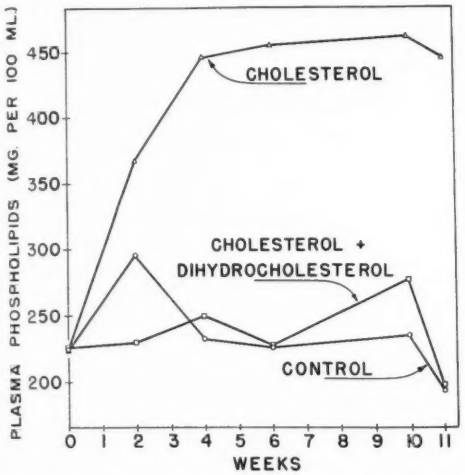

FIG. 3. Influence of dihydrocholesterol feeding upon plasma phospholipid levels of the cholesterol-fed chicken.

○—Average plasma phospholipid levels of eight birds fed a basal diet (Purina Broiler Chow plus 5 per cent Wesson Oil).

△—Average plasma phospholipid levels of eight birds fed a basal diet plus 1 per cent cholesterol.

□—Average plasma phospholipid levels of six birds fed a basal diet plus 1 per cent cholesterol plus 2 per cent dihydrocholesterol.

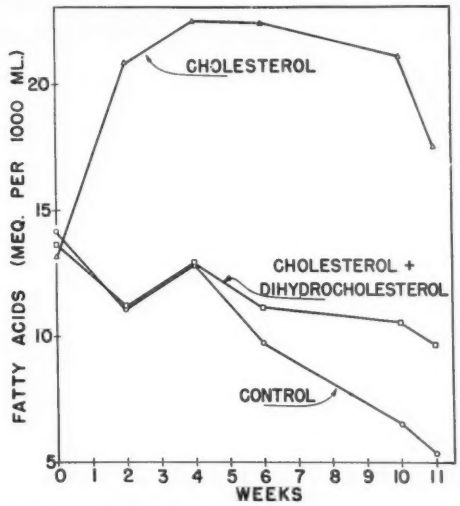

FIG. 4. Influence of dihydrocholesterol feeding upon plasma fatty acid levels of the cholesterol-fed chicken.

○—Average plasma fatty acid levels of eight birds fed a basal diet (Purina Broiler Chow plus 5 per cent Wesson Oil).

△—Average plasma fatty acid levels of eight birds fed a basal diet plus 1 per cent cholesterol.

□—Average plasma fatty acid levels of six birds fed a basal diet plus 1 per cent cholesterol plus 2 per cent dihydrocholesterol.

The addition of dihydrocholesterol to the cholesterol diet completely prevented the hyperlipemic effects of the cholesterol feeding. Not only did the plasma cholesterol levels in the birds of group 3 remain in the same range as those in the control birds, but, likewise, phospholipids and fatty acids failed to show any significant elevation. It should be noted that the effect of dihydrocholesterol is not due to a lower consumption of cholesterol and fat (table 1). Indeed, the total food intake of the dihydrocholesterol-fed birds (group 3) was actually slightly greater than that of birds fed cholesterol alone (group 2). Furthermore, the gain in weight (fig. 1) shown by the birds of group 3 was of the same order as that observed in the controls (group 1).

At the end of the 11 weeks, autopsies were performed on all birds. The aorta of each chicken was removed and examined for gross atheromata. Each lesion was carefully measured, and an estimate made of its area. The total areas of the atheromatous plaques of the thoracic and of the abdominal aortas were then calculated.

The effect of the dihydrocholesterol feeding on the development of atheromata in thoracic

and abdominal aortas in cholesterol-fed birds is shown in table 2. The prevention of the characteristic lesion, observed in both portions of the aortas, is quite striking. Thus the average area of grossly visible lesions in the thoracic portion of the aortas of the birds fed only cholesterol was 130 mm.^{2}, while five of the six birds that received dihydrocholesterol along with cholesterol showed no gross lesions whatsoever in this portion of the aorta. The average atheromatous lesion in the abdominal aorta of the birds fed cholesterol measured 50 mm.^{2}, whereas that in the birds fed dihydrocholesterol plus cholesterol was 9.5 mm.^{2} It should be noted that two of the birds fed the control diet showed atheromatous lesions. The average degree of severity of this group was 4.5 mm.^{2} and 0.5 mm.^{2} for thoracic and abdominal aortas respectively.

The significance of the experimental approach presented here to the control of plasma cholesterol, and possibly atherogenesis, in man is now under investigation.

TABLE 2.—*Effect of Dihydrocholesterol upon the Degree of Atherosclerosis in the Cholesterol-Fed Bird*

Bird no.	Diet	Gross atheromata found in:	
		Thoracic aorta	Abdominal aorta
		mm.^{2}	*mm.*^{2}
1	No cholesterol (group 1)	0	0
2	No cholesterol (group 1)	0	0
3	No cholesterol (group 1)	0	0
4	No cholesterol (group 1)	0	0
5	No cholesterol (group 1)	36	0
6	No cholesterol (group 1)	0	4
7	No cholesterol (group 1)	0	0
8	No cholesterol (group 1)	0	0
Average		4.5 mm.^{2}	0.5 mm.^{2}
9	1% cholesterol (group 2)	104	107
10	1% cholesterol (group 2)	142	51
11	1% cholesterol (group 2)	123	57
12	1% cholesterol (group 2)	0	25
13	1% cholesterol (group 2)	251	87
14	1% cholesterol (group 2)	140	10
15	1% cholesterol (group 2)	202	32
16	1% cholesterol (group 2)	81	27
Average		130 mm.^{2}	50 mm.^{2}
17	1% cholesterol + 2% dihydrocholesterol (group 3)	0	48
18	1% cholesterol + 2% dihydrocholesterol (group 3)	0	0
19	1% cholesterol + 2% dihydrocholesterol (group 3)	0	0
20	1% cholesterol + 2% dihydrocholesterol (group 3)	0	9
21	1% cholesterol + 2% dihydrocholesterol (group 3)	0	0
22	1% cholesterol + 2% dihydrocholesterol (group 3)	8	0
Average		1.3 mm.^{2}	9.5 mm.^{2}

SUMMARY

1. Birds fed a diet containing 1 per cent cholesterol developed characteristic lipemia with average plasma cholesterol values ranging from 665 to 948 mg. per 100 ml. during the 11 week period.

2. Simultaneous feeding of dihydrocholesterol with this 1 per cent cholesterol diet resulted in complete suppression of the lipemia. During the period of observation the average plasma cholesterol values varied from 120 to 179 mg.

per 100 ml. In control birds fed a stock diet containing no cholesterol, average values for plasma cholesterol ranged from 101 to 147 mg. per 100 ml.

3. The development of atherosclerosis in the cholesterol-fed birds was greatly inhibited by the simultaneous administration of dihydrocholesterol. Indeed no measurable difference in the extent of atherosclerosis was noted between birds fed the control diet and those fed cholesterol plus dihydrocholesterol.

Acknowledgment

The technical assistance of Mr. Jacob V. Sherokoff is gratefully acknowledged.

Sumario Español

El efecto de la adición de dihidrocolesterol a una dieta alta en colesterol se ha estudiado en pollos. Se ha mostrado que en esta especie el colesterol elevado en el plasma y la ateroesclerosis resultante se puede reducir a niveles normales con este procedimiento.

References

[1] Siperstein, M. D., Nichols, C. W., Jr., and Chaikoff, I. L.: Effects of ferric chloride and bile on plasma cholesterol and atherosclerosis in the cholesterol-fed bird. Science. In press.

[2] Peterson, D. W.: Effect of soybean sterols in the diet on plasma and liver cholesterol in chicks. Proc. Soc. Exper. Biol. & Med. **78:** 143, 1951.

[3] —, Nichols, C. W., Jr., and Shneour, E. A.: Some relationships among dietary sterols, plasma and liver cholesterol levels, and atherosclerosis in chicks. J. Nutrition **47:** 57, 1952.

[4] Sackett, G. E.: Modification of Bloor's method for the determination of cholesterol in whole blood or blood serum. J. Biol. Chem. **64:** 203, 1925.

[5] King, E. J.: The colorimetric determination of phosphorous. Biochem. J. **26:** 292, 1932.

[6] Bauer, F. C., and Hirsch, E. F.: A new method for the colorimetric determination of the total esterified fatty acids in human sera. Arch. Biochem. **20:** 242, 1949.

Reaffirmation of the Auriculoventricular Conduction System in Man

The Introduction of a Unique Technic for Its Serial Motion Picture Reconstruction

By JOHN L. READ, M.D., ERLING S. HEGRE, PH.D., AND SIMON RUSSI, M.D.

Gross and microscopic studies of the auriculoventricular conduction system were performed in 60 human hearts. A unique technic is introduced which will produce a photographic record of undistorted serial sections through a block containing the auriculoventricular node, auriculoventricular bundle and branches. By projecting the completed film as a motion picture, the course and changing relationships of component structures can be followed from level to level in uninterrupted sequence. The neurogenic versus the myogenic concept of cardiac conduction is reviewed at length.

THE current or myogenic concept of cardiac conduction postulates that the impulse to contraction in the human heart and that of various ungulates originates in the sinoauricular node located at the junction of the superior vena cava and the right auricle. Thence it spreads radially over the walls of the auricles to reach the ventricles via a single muscular auriculoventricular bundle of His[1] situated in the lower part of the interauricular septum. The latter stems from a distinct auriculoventricular node (node of Tawara[2]). This node has a number of connections with myocardial fibers of the right auricle. The auriculoventricular bundle divides into right and left branches which are distributed to the corresponding sides of the interventricular septum. This concept has been established by various investigators and is lent collateral support from findings in other mammals. Each bundle forms a widespread subendocardial network in man.

The myogenic versus the neurogenic theory of conduction has long posed a controversial question in cardiac physiology. Prior to 1893 there was no known muscular connection between the auricles and the ventricles of the mammalian heart. Because nerve elements passed over the auriculoventricular groove, it was assumed that the impulse to contraction was transmitted by way of the neurogenic route. In 1893 His[1] published his classic description of the auriculoventricular bundle. Shortly before this, Kent[3] described muscular bridges connecting the auricles with the ventricles. He also dissected out the auriculoventricular bundle but failed initially to recognize its significance. This was followed in 1906 by Tawara's description of the auriculoventricular node. Their findings were endorsed by the investigations of Keith and Flack,[4] Cohn,[5] Kent,[6, 7] King[8] and others. In 1907 Erlanger and Blackman,[9] observing aseptic technic, crushed the auriculoventricular bundle in dogs by means of a special clamp (Erlanger clamp) and thereby produced complete experimental heart block. The block persisted during the remaining life span of the dogs (320 to 340 days). In 1935 Kountz and his associates[10] sectioned the left bundle branch in human hearts which had been revived after death by perfusion of the heart and lungs in situ. Standard lead electrocardiograms revealed the pattern of bundle branch block. In the same year they produced bundle branch block in living monkeys.[11] Similar results in monkeys were achieved by Storm[12] in 1936. In conjunction with their work on revived human hearts, Kountz and associates[13] attempted to explain the difference between

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the human electrocardiographic pattern of bundle branch block and the so-called classic interpretation derived from studies on canine hearts. This difference had been recognized by Barker, Macleod and Alexander,[14] Oppenheimer and Pardee,[15] Farr,[16] and others. Kountz found that with the dog assuming its usual posture, the heart lay anteriorly and electrocardiograms so obtained were similar to those of man. In the experimental positions, however, with the chest open and the dog on its back, the heart falls posteriorly a considerable distance in the mediastinum and rotates clockwise. The human chest does not allow for such marked changes in heart position. The beating dog's heart was next placed within the pericardial cavity of a human cadaver and electrocardiograms obtained were again similar to those from the human heart.

Thus, it was established that the auriculoventricular bundle represents the sole pathway by which the cardiac impulse is conveyed from auricle to ventricle; further, that the A-V bundle does not regenerate. In 1925, using electrocardiographic methods, Lewis[17] demonstrated a difference in the rate of conduction in various cardiac fibers. He found the speed of conduction to be proportional to the glycogen content and fiber size but inversely proportional to the rhythmicity and refractory period. Conduction time varied from 0.2 meters per second in the small nodal fibers to 4.0 meters per second in the Purkinje fibers.

The myogenic theory remained firmly established until 1940 when Glomset and associates,[18-21] in a series of papers, challenged the myogenic in favor of the neurogenic concept. They agree with the existence of a myogenic system in sheep, cattle and swine, but not in man, dog, and the horse where they feel that the system is vestigial and does not mediate conduction. They conclude as follows: (1) There is no distinct A-V node; (2) the bundle of His is structurally identical with other muscle fasiculi; it has no left branch and therefore does not bifurcate; (3) the ridge fasiculus (bundle of His) has no special vascular supply; (4) there is no muscular connection between the fibers of the ridge fasiculus and the right auricle; (5) in dog and man, all elements identified as Purkinje fibers are ordinary muscle fibers which have been altered slightly by their environment in regions where the bundle and its branches are supposed to exist; (6) the amount of glycogen revealed by staining with iodine and Best carmine does not constitute a distinguishing feature of the Purkinje fiber; (7) the vesicular, hollow or vacuolated appearance of the Purkinje fiber represents an artifact; nowhere did they find evidence of transition from Purkinje fiber to ordinary cardiac muscle fiber; (8) there is no anatomic evidence to support the myogenic theory of cardiac conduction.

Finally, they state: "We therefore believe that the cardiac musculature is under a nervous control similar to that of other muscle tissue and consider it physiologically unsound to draw conclusions concerning cardiac conduction without taking cognizance of the rich intrinsic nerve system of the heart."

Faced with these apparently heretical observations, the exponents of the myogenic thesis renewed their investigations. Since the work of Glomset and coworkers, a series of studies of human and mammalian embryos has tended to reaffirm the myogenic hypothesis.

Walls[22] studied serial sections of human embryos in an attempt to determine whether the conducting tissue developed as other organs of the body or are simply remnants of junctional tissues found at the sinoauricular and auriculoventricular rings. He concluded that, "The bundle is a new formation which arises from that primitive nodal tissue by a process of active growth." This view is also adhered to by Tandler,[23] Retzer,[24, 25] Shaner,[26] and Davies.[27]

Structural differentiation of the human heart was found to commence at the 8 mm. stage, the auriculoventricular node and bundle of His being formed in advance of the sinoauricular node. The auriculoventricular node extends from a position behind the dorsal endocardial cushion to reach the crest of the interventricular septum where it bifurcates. The sinoauricular node appears at the 10 mm. stage and nerve elements at the 20 mm. stage. Function begins before the appearance of nerve elements. In studies on living rat embryos, Goss[28] ob-

served the initial activity of contraction to occur at the two somite stage in the left heart just to the ventricular side of the A-V junction at a regular rate of 32 to 42 beats per minute. This was followed in a few hours by contractions from the corresponding area of the right side so that the ventricles contracted asynchronously. By the eight somite stage, however, the tardier sinoauricular node became the pacemaker, initiating contractions 0.1 to 0.2 second before the ventricles with a consequent increase in rate. Patten and Kramer[29] (1933) had made similar observations in the living chick embryo. They point out that the change of pacemaker occurs before any neuroblasts approach the heart.

In 1948 Robb and Kaylor[30] carried out a detailed study of the specialized tissue of the human fetal heart at various stages of development. Their observations on the distribution of the specialized cells of the A-V system were somewhat at variance with those of Tawara[2] and Monckeberg[31] who reported that specialized fibers to the septal and lateral walls arose from recurrent branches in the apical regions. The authors found that the specialized cells of the A-V system also occurred throughout the septum. They stress the importance of this finding on the present day interpretation of electrocardiograms. The constant appearance of more than one right branch is also emphasized and its possible relation to the Wolff-Parkinson-White[32] syndrome is discussed. The authors hesitate in their acceptance of the myogenic theory on the grounds that complete knowledge is lacking concerning the exact pathways, terminations and function of sympathetic nerves which accompany the bundle and branches. The pathways of the parasympathetic nerves, however, have been superbly demonstrated by Nonidez.[33] They mention the present day tendency to overlook this gap in our knowledge and state:

"We must realize that the exclusive allocation of the function of the specialized cells depends on one type of experiment. The method was to cut or crush the bundle and allow the animals to recover. The assumption was made that if the conducting tissue were nerve, regeneration would not occur and the block would be permanent. The comment may be made that scar tissue barriers may prevent peripheral regeneration of axones. Such barriers are present following cutting, crushing, ligation, or injection experiments at the base of the heart. Thus we may say the presumptive (but not the absolutely proven) opinion is that the specialized tissue is the ordinary conducting pathway from auricle to ventricle. At times this pathway probably yields to one consisting of ordinary muscle fibers."

Davies and Francis[34] approached the problem from the ontogenic viewpoint in poikilo- and homothermic vertebrates and concluded that nodal and Purkinje fibers represent neomorphic developments in the hearts of mammals and birds, whereas in poikilothermic vertebrates, there is no specialization of cardiac muscle fibers. They postulate a differential distribution in the various chambers of certain chemicals known to affect muscular contraction to be responsible for the ordered function of the poikilothermic heart.

It has been shown that the foundation for the myogenic concept rests upon a number of conclusive anatomic and physiologic investigations. Most important has been the observation that the conduction system is composed of modified muscle or Purkinje[35] tissue. In 1947 Truex and Copenhaver[36] reviewed the literature and made a detailed study of Purkinje fibers from the hearts of man and various mammals. They successfully resolved many of the controversial problems pertaining to the structure and identification of these fibers in man. They describe Purkinje fibers as containing fewer myofibrillae but more interfibrillae and interfibrillar sarcoplasm, which accounts for their clearer, less compact appearance. The center of the fiber is devoid of myofibrillae and is filled with a granular sarcoplasm in which the nuclei are seen usually in groups of two or more. Purkinje fibers were identified most easily by the Azan and Masson technic in sheep, pigs, calves and cattle. In these species, the bluish appearance of the cytoplasm contrasted sharply with the more intense reddish staining of ordinary cardiac muscle. The number of fasicles also represented a distinguishing feature. These criteria proved of little value in cats, monkeys and man where the singly arranged Purkinje fibers did not always stain differentially and

lacked a continuous connective tissue sheath to delimit them from adjacent muscle. In fact, this sheath is so well developed in the ungulates, that it has been studied extensively by the injection of various dyes.[5, 8, 37–41] However, with higher magnification the larger Purkinje fibers in man were readily identified by their clear central area and sparse peripherally placed myofibrillae. They were able to identify Purkinje fibers in 14 of 20 human hearts. Because of an evident overlap in the diameter of Purkinje and cardiac muscle fibers, they computed an average measurement on the basis of 25 fibers of each. Only those fibers were selected which included nuclei in the plane of the section and these were measured in their widest portions. Purkinje fibers were found to be twice the mean diameter of cardiac fibers in all animals except man. In cattle the cardiac fibers averaged 15.5 microns as compared to 43.6 microns for the Purkinje fibers, whereas in man, the comparison was 16.1 to 20.6 microns. Examination of longitudinal sections revealed regions of continuity between Purkinje and cardiac fibers. Purkinje fibers stained with Best carmine glycogen consistently revealed an excess of glycogen. They emphasize the state of tissue preservation in specimens to be studied and conclude that much of the confusion over this subject arises from a failure to appreciate individual and species difference of Purkinje fibers. The so-called "typical Purkinje fiber" is a popular fallacy, since it is often based on the appearance of the typical fiber in another species.

Materials, Methods and Findings

Macroscopic studies. The auriculoventricular conduction system was dissected out in a total of 50 human hearts from an average age group of 40 years. Forty hearts were examined after fixation in formalin. The remainder were examined unfixed. Dissections were performed with the aid of a binocular dissecting microscope at a magnification of seven diameters. The auriculoventricular node, auriculoventricular bundle, and right bundle branch were located with ease. Considerable care, however, was necessary in defining the left bundle branch.

Microscopic studies. Four adult hearts were examined by consecutive serial sections. Six others were studied by taking a series of sections through areas known to contain the component structures of the conduction system.

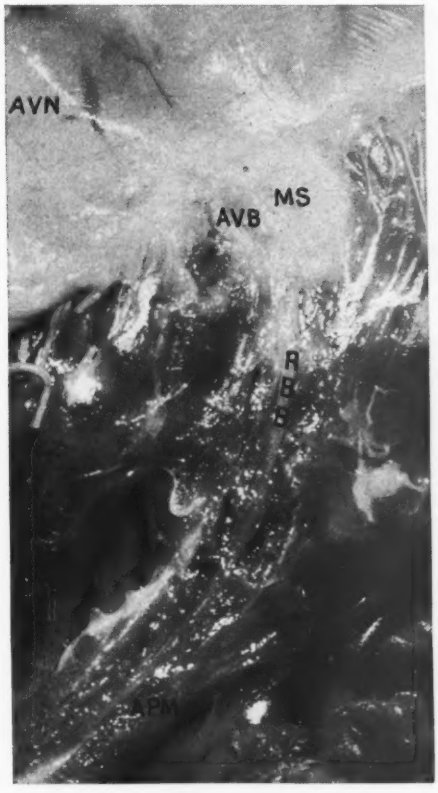

Fig. 1. Photograph of dissection of the auriculoventricular node, auriculoventricular bundle, and the right bundle branch of the unfixed human heart (approximately ×4). Viewed from the right side of the interventricular septum and demonstrating the anterior papillary muscle. AVN, auriculoventricular node; AVB, auriculoventricular bundle (bundle of His); RBB, right bundle branch; MS, membranous portion of the interventricular septum; TV, tricuspid valve; RVS, right ventricular septum.

All hearts studied were essentially normal except for a few with moderately severe atherosclerosis. Serial blocks were cut through the crest of the auriculoventricular septum and along the course of the bundle branches. Sections were 8 to 12 microns in thickness. Sec-

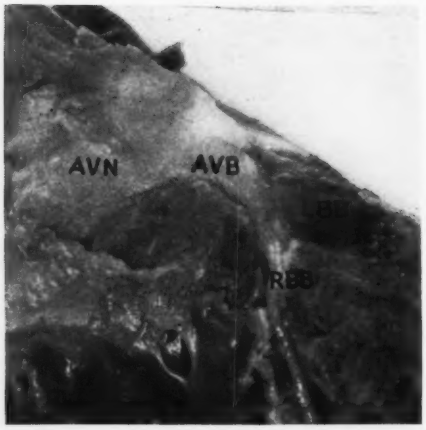

FIG. 2. Photograph of dissection of the auriculoventricular node and auriculoventricular bundle which demonstrates the bifurcation of the auriculoventricular bundle of the normal adult human heart following formalin fixation (approximately ×4). AVN, auriculoventricular node; AVB, auriculoventricular bundle; LBB, left bundle branch; RBB, right bundle branch; TV, tricuspid valve; RVS, right ventricular septum.

FIG. 3. Photomicrograph of the auriculoventricular node in cross section (×16). Van Gieson's stain. AVN, auriculoventricular node.

tions were stained with hematoxylin and eosin except for every fifth section which was stained by the Van Gieson method.

The auriculoventricular node is roughly flask-shaped and is located on the right side of the interauricular septum between the orifice of the coronary sinus and the right border of the membranous septum of the ventricle (figs. 1 and 2). It measures approximately 8 by 4 by

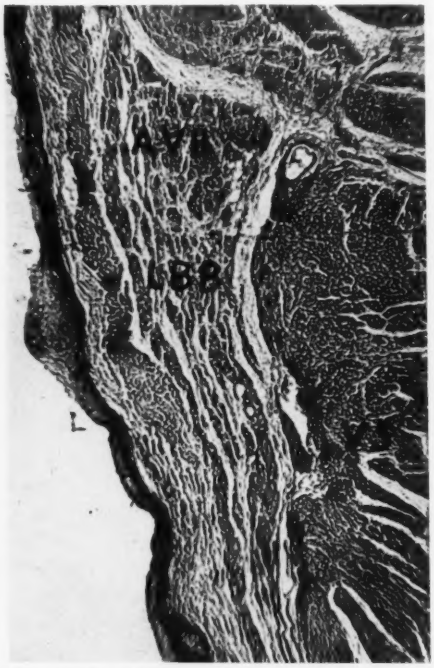

FIG. 4. Photomicrograph of the left bundle branch leaving the auriculoventricular bundle, in cross section (×16). Van Gieson's stain. LBB, left bundle branch; AVB, auriculoventricular bundle; VS, ventricular septum.

0.6 mm. The node converges toward, and its anterior portion penetrates, the central fibrous body (trigonum fibrosum) where it forms a slender muscle bundle, the bundle of His, which measures 1 to 4 mm. in width and approximately 15 to 20 mm. in length. The bundle is roughly triangular on cross section. It bridges the crest of the interventricular septum within the lower part of the membranous septum of the ventricle and just below the mesial portion of the aortic fibrous ring. Just before reaching the left border of the membranous septum, it

bifurcates (fig. 2). The right bundle branch dips caudally beneath the tricuspid valve in the groove between the mesial and anterior cusps (fig. 1). It descends to enter the myocardium of the right side of the septum (fig. 5), gradually emerging so that it becomes subendocardial at the base of the anterior papillary muscle (fig. 1) where it is often visible to the naked eye. Frequently the overlying muscle bundles of the myocardium run obliquely across it, thus helping to define it more clearly. The right bundle seems to form a continuous arc which merges imperceptibly into the bundle of His. It measures approximately 1.5 mm. in width and averages about 40 mm. in length. The left branch (fig. 2) forms a broad membranous ribbon 3 to 6 mm. in width as it leaves the bundle below the aortic fibrous ring and just to the right of the right semilunar valve of the aorta and becomes almost immediately subendocardial. It blends so intimately with this lining that it is most difficult to dissect out intact. As it descends, it gradually fans out into numerous diverging fasiculi and is somewhat longer than the right branch. In most hearts, the left branch divides into an anterior and posterior ramus. These observations are in accord with recent observations of Kisten[42] and Lev.[43, 44]

The auriculoventricular node (fig. 3) appears as a compact mass of fine interlacing muscle fibers which are roughly ovoid in transverse section. These fibers are smaller than those of the adjacent auricle. The fibers of the auriculoventricular bundle (fig. 4) are somewhat larger than those of the auriculoventricular node but smaller than those of the ventricular myocardium and stain somewhat paler. As the bundles descend, more and more Purkinje fibers (fig. 6) make their appearance.

One of us (E.S.H.)[45, 46] devised a unique apparatus (fig. 7) which will produce a photographic record of undistorted serial sections at 6 micron intervals through a block of tissue containing the auriculoventricular node, bundle of His, and bundle branches. By project-

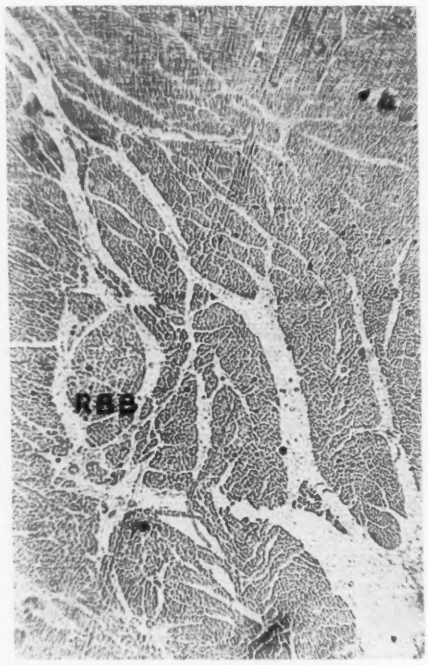

FIG. 5. Photomicrograph of the right bundle branch in cross section (×16). Hematoxylin and eosin. RBB, right bundle branch.

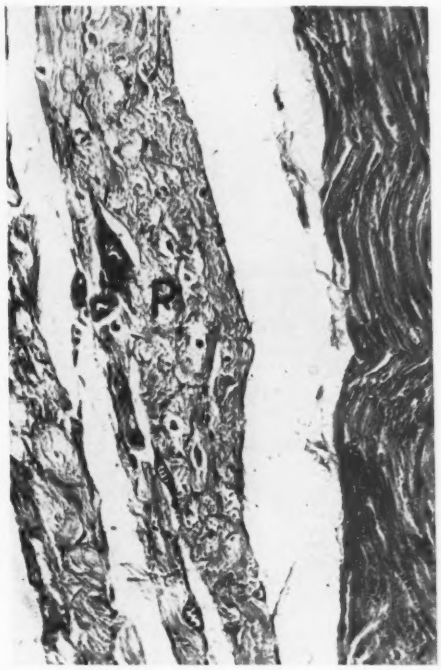

FIG. 6. Photomicrograph of Purkinje fibers in oblique section (×100). Van Gieson's stain. Ordinary cardiac muscle is seen to the right. P, Purkinje fibers.

ing the completed film as a motion picture, it is possible to follow the course and changing relationships of the component structures from level to level in an uninterrupted sequence. Specimens which have been fixed in formalin are immersed in a solution of 80 per cent alcohol in which 2 Gm. of lead acetate per 100 cc. have been dissolved (eight hours). They are then transferred to 95 per cent alcohol containing 0.5 Gm. of lead acetate per 100 cc. Dehydration is completed in the usual manner with minor modifications. The tissue (fig. 7 *a*) is mounted in the vise of a sliding knife microtome. The knife is mounted at one end of the sliding carriage and is equipped with a suction tube (*b*) which will remove and dispose of each section as it is cut. Any or all sections may be saved if desired for study at high magnifications. The vacuum line is compressed by a normally closed clamp (*c*) which is released by a dog (*d*) at the proper interval. The stain is conducted by gravity from a reservoir through a rubber tube to a small channel in a plastic bar (*e* and *e'*). The fluid emerges through a small pore on the under surface of the bar where it slowly accumulates to form a hanging drop. A second and similar channel in this plastic bar is attached to a water siphon and will remove the excess stain. The plastic bar is mounted on the sliding carriage in such a way that it will pass directly over the specimen with a clearance of a fraction of a millimeter. Thus the stain will in turn be applied to the tissue held in contact for a time and then removed at appropriate intervals of the cycle. The specimen is illuminated by the filtered light from two spot lights. A Cine Kodak special 16 mm. motion picture camera is mounted above the block. The shutter release is electrically actuated as a revolving brush (*h*) passes over each exposed contact in an armature (*g*). Thus at the proper interval, a predetermined

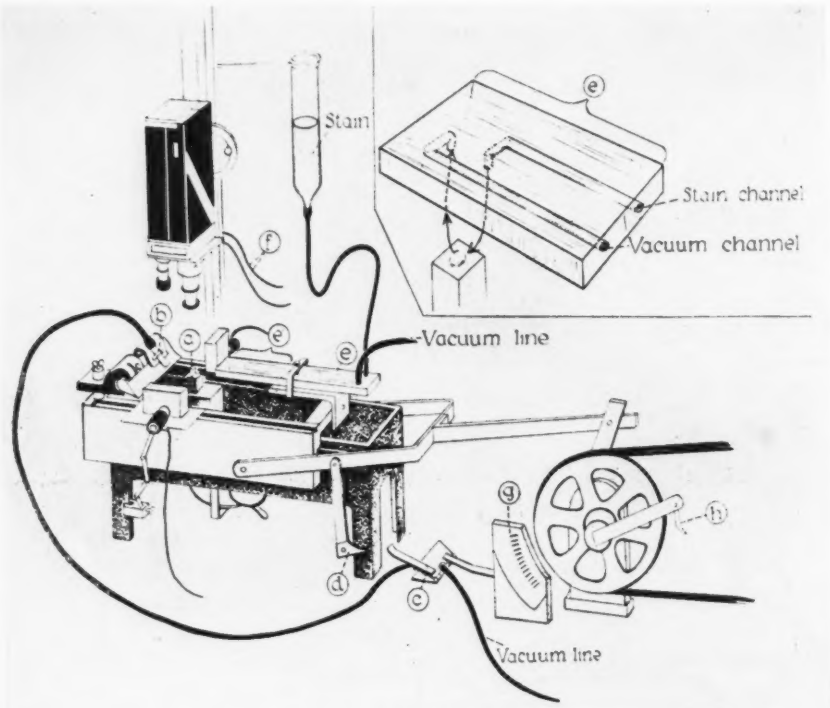

FIG. 7. Diagram of apparatus for making a motion picture record of consecutive serial sections through the conducting tissue.

number of exposures can be made at each new level. The whole apparatus is powered by a one third horse power electric motor.

The essential procedure embodies a distinct departure from the usual method of preparing and studying serial sections, that is, the stain is applied not to the displaced sections, but to the intact surface of the block. Attention can therefore be directed to the details of the exposed surface in their normal relationship to the remainder of the specimen. Furthermore, serial sections prepared by routine methods always suffer some distortion due to compression during cutting or as a result of inequal spreading. Such inaccuracies do not occur with the present method. The resultant section is stained in varying shades of sepia due to the lead sulfide precipitated by the action of the sodium sulfite staining solution upon the lead acetate impregnated tissue.

A motion picture of the conduction system was prepared by this technic. The film allows one to follow the course of the bundle of His as it leaves the auriculoventricular node, crosses the septum and then bifurcates. The bifurcation is depicted rather dramatically. As the last section of overlying tricuspid valve is removed, the right branch makes its appearance and the bundle and both branches are revealed.

Discussion

Despite the question posed by Glomset and his associates, the accumulated evidence tends to reaffirm the myogenic theory of conduction. Due to inadequate nerve-staining technics, the exact distribution of the sympathetic (in particular) and parasympathetic nerve fibers to the heart has not been established sufficiently well to prove or disprove either theory. Nettleship[47] and Hirsch[48] reported on the extent of nerve degeneration following ganglionectomy in lower animals. The former demonstrated degeneration and fragmentation of ventricular nerve trunks and the ventricular epicardial network following bilateral stellate and middle cervical ganglionectomy. Similar structures in the auricles were spared. There also occurred degeneration of the apical portion of the endocardial plexus, simple nerve endings in the fat and from one half to three fourths of the coronary artery plexuses. Thoracic dorsal root ganglionectomy produced similar changes. Following total vagotomy, the epicardial plexus of the ventricle was spared, but degeneration occurred in the auricular trunks, endocardial, aortic and pulmonary plexuses. Section of the vagus proximal to the nodose ganglion spared myelinated fibers of the auricles but not those terminating about the epicardial ganglia. Electrocardiographic studies were not a part of these experiments. The fact that similar procedures are performed in man for various reasons without any resultant heart block would seem to discount the neurogenic mode of conduction. Logically it would appear highly improbable that conduction should be mediated through the muscular route in practically all animals except man. One might hypothesize that in view of the unique function of the heart which requires its fibers to lengthen and shorten forcefully approximately 100,000 times each day, that the most efficient mode of conduction might occur in a tissue which is also capable of such changes in length without interfering with its conducting function.

The authors feel that the technic described herein demonstrates more clearly than any other the cardiac conduction system. The motion picture record clearly refutes certain of the morphologic claims of the neurogenic exponents. This technic will be applied in subsequent studies in an attempt to demonstrate in moving sequence the histologic picture of bundle branch block and the vascular supply to the conducting tissue.

Summary

The question and evolution of the myogenic versus the neurogenic theory of cardiac conduction is reviewed at length.

Gross and microscopic studies of the auriculoventricular conduction system were carried out in a total of 60 adult human hearts. Results of these studies are in accord with the myogenic concept of cardiac conduction.

Sumario Español

Estudios gruesos y microscópicos del sistema de conducción aurículoventricular fueron obtenidos en 60 corazones humanos. Una técnica

única es introducida que produce un record fotográfico serial en secciones no distorcionadas de un bloque conteniendo el nódulo aurículoventricular, el paquete aurículoventricular y sus ramificaciones. Proyectando la película terminada como una cinta cinematográfica el curso y las relaciones variables de las estructuras del componente pueden ser observadas de un nivel a otro en una sequencia no interrumpida. El concepto miogénico de conducción cardíaca y el concepto neurogénico son revisados en detalle.

REFERENCES

[1] His, W., Jr.: Die Thaetigkeit des embryonalem Herzens und deren Bedeutung fuer die Lehr von der Herzbewegung beim Erwachsenen. Arb. med. Klin. zu Leipz, 1893. P. 14.

[2] Tawara, S.: Das Reitzleitungssystem des Saeugetierherzens. Jena, Gustav Fischer, 1906.

[3] Kent, A. F. S.: Researches on the structure and function of the mammalian heart. J. Physiol. **14:** 233, 1893.

[4] Keith, A., and Flack, M. W.: The auriculoventricular bundle of the human heart. Lancet **2:** 359, 1906.

[5] Cohn, A. E.: Demonstration of ox hearts showing injection of the conduction system. Proc. New York Path. Soc. **11:** 130, 1911.

[6] Kent, A. F. S.: The structure of cardiac tissues at the auriculoventricular junction. Proc. Physiol. Soc. (Nov. 15) 1913. J. Physiol. **47:** 17, 1913.

[7] —: Neuromuscular structure in the heart. Proc. Roy. Soc. London, S. B. (Biological Sciences) **87:** 198, 1914.

[8] King, M. R.: The sinoventricular system as demonstrated by the injection method. Am. J. Anat. **19:** 149, 1916.

[9] Erlanger, J., and Blackman, J. R.: A study of relative rhythmicity and conductivity in various regions of the auricles of the mammalian heart. Am. J. Physiol. **19:** 125, 1907.

[10] Kountz, W. B., Prinzmetal, M., Pearson, E. F., and Koenig, K. F.: The effect of position of the heart on the electrocardiogram. I. The electrocardiogram in revived perfused human hearts in normal position. Am. Heart J. **10:** 605, 1935.

[11] —, —, and Smith, J. R.: The effect of position of the heart on the electrocardiogram. III. Observations upon the electrocardiogram in the monkey. Am. Heart J. **10:** 623, 1935.

[12] Storm, C. J.: Over Ventriculaire Extrasystolen en here Locatisatee. Batavia, G. Kolff & Co., 1936.

[13] Kountz, W. B., Prinzmetal, M., and Smith, J. R.: The effect of position of the heart on the electrocardiogram. II. Observations upon the electrocardiogram obtained from a dog's heart placed in the human pericardial cavity. Am. Heart J. **10:** 614, 1935.

[14] Barker, P. S., MacLeod, A. G., and Alexander, J.: Excitatory process obtained in the human heart. Am. Heart J. **5:** 720, 1930.

[15] Oppenheimer, B. S., and Pardee, H. E. B.: The site of the cardiac lesion in two instances of intraventricular heart block. Arch. Int. Med. **17:** 177, 1920.

[16] Farr, G.: Spread of the excitatory wave. Arch. Int. Med. **25:** 146, 1920.

[17] Lewis, T.: Mechanism and Graphic Registration of the Heart Beat, ed. 3. London, Shaw & Sons, 1925. P. 159.

[18] Glomset, D. J., and Glomset, A. T. A.: A morphologic study of the cardiac conduction system in ungulates, dog and man. Part I: The sinoatrial node. Am. Heart J. **20:** 387, 1940.

[19] —, and —: A morphologic study of the cardiac conduction system in ungulates, dog and man. Part II: The purkinje system. Am. Heart J. **20:** 677, 1940.

[20] —, and Birge, R. F.: A morphologic study the cardiac conduction system. Part IV: The anatomy of the upper part of the ventricular septum in man. Am. Heart J. **29:** 526, 1945.

[21] —, and —: A morphologic study of the cardiac conduction system. Part V: The pathogenesis of heart block and bundle branch block. Arch. Path. **45:** 135, 1948.

[22] Walls, E. W.: The development of the specialized conducting tissue of the human heart. J. Anat. **81:** 93, 1947.

[23] Tandler, J.: Manual of Human Embryology. Philadelphia, Lippincott, 1912.

[24] Retzer, R.: Some results of recent investigations on the mammalian heart. Anat. Rec. **2:** 149, 1908.

[25] —: The sinoventricular bundle; a functional interpretation of morphological findings. Contr. Embryol. Carnegie Institution **9:** 143, 1920.

[26] Shaner, R. F.: The development of the atrioventricular node, bundle of His and sinoauricular node in the calf; with the description of a third embryonic node-like structure. Anat. Rec. **44:** 85, 1929–1930.

[27] Davies, F.: The conducting system of the vertebrate heart. Brit. Heart J. **4:** 66, 1942.

[28] Goss, C. M.: The physiology of the embryonic mammalian heart before circulation. Am. J. Physiol. **137:** 146, 1942.

[29] Patten, B. M., and Kramer, T. C.: The initiation of contraction in the embryonic chick heart. Am. J. Anat. **53:** 349, 1933.

[30] Robb, J. S., and Kaylor, C. T.: A study of specialized heart tissue at various stages of development of the human fetal heart. Am. J. Med. **5:** 324, 1948.

[31] Monckeberg, J. G.: Untersuchungen über das

Atrioventriklar-Bundel im menschlichen Herzen. Jena, Fischer, 1908.

[32] WOLFF, F., PARKINSON, J., AND WHITE, P. D.: Bundle branch block with a short P-R interval in healthy young people prone to paroxysmal tachycardia. Am. Heart J. **25:** 454, 1943.

[33] NONIDEZ, J. F.: The structure and innervation of the conductive system of the heart of the dog and rhesus monkey as seen with a silver impregnation technique. Am. Heart J. **26:** 577, 1943.

[34] DAVIES, F., AND FRANCIS, E. T. B.: The conducting system of the vertebrate heart. Biol. Reviews **21:** 173, 1946.

[35] PURKINJE, J. E.: Microscopisch-Neurologische Beobachtungen. Arch. Anat., Physiol., u. wissench. Med. **12:** 281, 1845.

[36] TRUEX, R. C., AND COPENHAVER, W. M.: Histology of the moderator band in man and other mammals with special reference to the conduction system. Am. J. Anat. **80:** 173, 1947.

[37] COHN, A. E.: Observations on injection specimens of the conduction system in ox hearts. Heart **4:** 225, 1913.

[38] LHAMON, R. M.: The sheath of the sinoventricular bundle. Am. J. Anat. **13:** 55, 1912.

[39] AAGAARD, O. C., AND HALL, Y. C.: Ueber injektionen dis "Reitzleitungssystems" und der lymphgefaesse dis saeugetierherzens. Anat. Hefte **51:** 357, 1914.

[40] CARDWELL, J. C., AND ABRAMSON, D. I.: The atrioventricular conduction system of the beef heart. Am. J. Anat. **49:** 167, 1931.

[41] ABRAMSON, D. I., AND MARGOLIN, M. A.: A Purkinje conduction network in the myocardium of the mammalian ventricles. J. Anat. **70:** 250, 1936.

[42] KISTEN, A. D.: Observations on the anatomy of the atrioventricular bundle (bundle of His) and the question of other muscular atrioventricular connections in normal human hearts. Am. Heart J. **37:** 849, 1949.

[43] LEV, M., WIDROW, J., AND ERICKSON, E. E.: A method for the histopathologic study of the atrioventricular node, bundle, and branches. Arch. Path. **52:** 73, 1951.

[44] WIDRAN, J., AND LEV, M.: The dissection of the atrioventricular node, bundle and bundle branches in the human heart. Circulation **4:** 863, 1951.

[45] HEGRE, E. S., AND BRASHEAR, A. D.: The block surface method of staining as applied to the study of embryology. Anat. Rec. **97:** 21, 1947.

[46] —: A new research tool and technique for the biologist. Virginia J. Science **2:** 10, 1951.

[47] NETTLESHIP, W. A.: Experimental studies on the afferent innervation of the cat's heart. J. Comp. Neurol. **64:** 115, 1936.

[48] HIRSCH, E. F., AND ORINE, J. F.: Sensory nerves of the human heart. Arch. Path. **44:** 325, 1947.

1-Hydrazinophthalazine (Apresoline in the) Treatment of Hypertension: A Two Year Study

By JOSEPH H. HAFKENSCHIEL, M.D., AND M. AUGUST LINDAUER, M D.

Patients with severe essential hypertension have been carefully studied periodically in an attempt to group them as to probable life expectancy. Forty such patients have been observed while on oral 1-hydrazinophthalazine and a low salt diet. Nineteen of the 33 patients in the groups having a relatively good prognosis for survival had some decrease in diastolic pressure. Only one of seven patients in Smithwick group IV had a satisfactory reduction in blood pressure.

THIS REPORT concerns our experience during a period of two years with 1-hydrazinophthalazine (Apresoline) and a low salt diet in 40 patients. All have been on this program for at least one year. They have been grouped as to life expectancy, according to Smithwick's classification.[1]

A comparison of survival rates after thoracolumbar sympathectomy, and after medical therapy in similar hypertensive patients, suggests that surgical treatment may improve the group life expectancy of patients with certain severe vascular complications (Smithwick group IV).[1-3] Following sympathectomy, however, the number of patients who are dead five years after operation is high.[1] We were particularly interested in those patients who might be expected to do poorly with sympathectomy. Could these be benefited by any one, or a combination, of the newer depressor drugs?[4, 5]

The depressor properties of Apresoline were discovered in the course of testing of antimalarial drugs.[6] The reduction of both systolic and diastolic pressure in animals, by an action largely central, without a sedative component, led to measurements of renal blood flow during the hypotension induced by parenteral doses of the drug in both normotensive and hypertensive patients.[7] The increase in renal blood flow observed in hypertensive patients was followed by studies of the influence of this drug on vasoconstrictor reflexes in man.[8] Apresoline appears to suppress the outflow of sympathetic vasopressor impulses.

We observed a reduction of blood pressure both supine and standing after intramuscular injection[4] and an increased renal blood flow in an acute experiment in one patient with azotemia[9] (table 1). A decreased cerebral vascular resistance was obtained in seven patients with moderate hypertension[10] (table 2). These acute experiments led to a prolonged study of the oral effectiveness of 1-hydrazinophthalazine in patients with essential hypertension.

METHODS

Forty outpatients were evaluated in the fashion previously reported.[5, 11] All were placed on Apresoline plus a salt restricted diet for at least one year. Sufficient observations and repetition of tests were made to permit grouping as to life expectancy according to the criteria of Smithwick.[1] The number of patients of both sexes in each of the four groups is shown in table 3.

Those who have continued to take the drug for at least one year have been evaluated by monthly visits to the Hypertension Clinic. The morning dose of the drug was ingested about one hour before reporting to clinic. At each clinic visit the blood pressure was checked after a 10-minute rest, using a postural test.[12] At six-month intervals the following examinations were repeated: retinoscopy, electrocardiogram, orthodiagram, intravenous phenol-

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TABLE 1.—*Effect of an Intramuscular Injection of 20 mg. of Apresoline on Renal Hemodynamics and Mean Arterial Pressure in a Young Male (Smithwick Group IV) with Mild Azotemia**

	Before Apresoline	90 Minutes After Apresoline
BUN	30	
Urea Clearance	50	
Plasma Creatinine	1.7	
Creatinine Clearance	55	52
PSP	10% in 15 minutes	
CPAH	195	250
Renal Blood Flow	295	380
Mean Blood Pressure	130	115
Filtration Fraction	.28	.21
Renal Peripheral Resistance	.45	.30

* These studies indicate a rise in renal blood flow and a fall in renal peripheral resistance.

This study was performed by Drs. John K. Clark and A. P. Crosley and was supported in part by the National Heart Institute, U. S. Public Health Service.

TABLE 2.—*Effect of Intramuscular Injection of 10 to 20 mg. of Apresoline on Cerebral Hemodynamics and Oxygen Metabolism in Patients with Minimal Vascular Complications 60 Minutes after the Initial Study*†

	Pressure		Flow		Resistance		Uptake	
	Before	After	Before	After	Before	After	Before	After
8 Obsns. 7 patients	144	113	56	57	2.8	2.1	3.6	3.2
Change after Apresoline	31 ± 20		1 ± 15		0.7 ± 0.5		0.4 ± 0.9	
	$p < 0.01$				$p < 0.01$			

† Pressure was measured by a damped mercury manometer through the indwelling femoral artery needle. The figures in the first horizontal line on the left are the group averages during the initial study and 60 minutes after Apresoline. Cerebral blood flow and oxygen uptake were measured by the nitrous oxide technique of Kety and Schmidt. Resistance is the pressure divided by flow. The figures in the second horizontal line of each column represent the mean change and the standard deviation of the individual differences. The only statistically significant reductions were in the mean arterial pressure and cerebral vascular resistance.

sulfonphthalein (PSP) test, urinalysis, hemoglobin and leukocyte count, and blood urea nitrogen (if elevated initially).

Dosage Schedule. Most patients were started on a dose of 25 mg. four times daily. The dose was increased gradually until either a satisfactory fall in blood pressure was obtained, or a maximum dose of 200 mg. four times daily was reached. The effective dose ranged from 75 mg. to 200 mg. repeated either three or four times daily. The average dose was 125 mg. four times daily, as noted by Grimson.[13]

Placebo Medication. Inactive tablets were substituted for Apresoline in six cases for periods of from one to two months. In each instance, there was a rise in both systolic and diastolic pressures. Reduction to the former level was observed when the previous dosage of Apresoline was again reached (figure 1). It is our observation that, upon returning to Apresoline, small dosages should be used and gradually increased. There is apparently an unusual susceptibility to side reactions at this time.

TABLE 3.—*Number of Patients of Each Sex in Groups According to Smithwick Who Were on Apresoline for One Year or More*

Smithwick Group	Males	Females
I	2	7
II	10	7
III	5	2
IV	4	3
	21	19

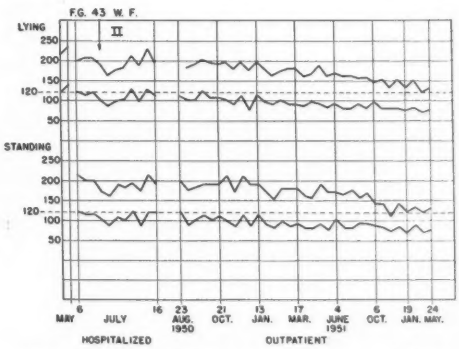

FIG. 1. Blood pressure observations, supine and standing, for three minutes in a female patient of group II having a satisfactory reduction while on oral Apresoline for 24 months. Treatment was initiated while the patient was hospitalized as denoted by the arrow. The peaks in pressure late in this period were observed when Apresoline was withheld so that laboratory tests could be performed.

Results

Depressor Properties. The effects upon blood pressure in relation to the Smithwick classification are presented in table 4. There were 9 patients in group I, 17 in group II, 7 in group III and 7 in group IV.

Improvement in blood pressure was arbitrarily considered to have occurred if there was a fall in *supine diastolic pressures* from 120 mm. Hg or higher to 110 mm. or lower on at least two outpatient visits. The majority of

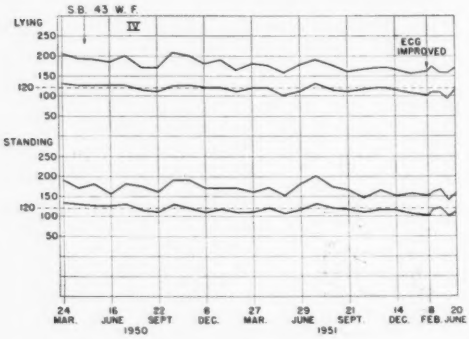

FIG. 2. Blood pressure observations, supine and standing, in a female patient of group IV having a satisfactory reduction while on oral Apresoline for 23 months. The arrow designates when the patient was started on the drug. The electrocardiogram repeated periodically during the interval on the drug was observed to be improved at the twenty-third month. This finding coincided with lower blood pressures and symptoms suggesting that the blood pressure was too low. The dosage of Apresoline was reduced at this time.

these patients before treatment had diastolic pressures above 130 mm. Hg.

Fifteen out of 26 in group I and II showed this degree of fall in blood pressure. The favorable response of a group II patient is shown in figure 1. In group III there were favorable reductions in four of seven patients, and in group IV, in only one of seven. The blood pressure response of this latter patient is shown in figure 2. The fall in blood pressure after three minutes of quiet standing was not strikingly different from the resting blood pressure in any of our patients.

Evidence of Clinical Improvement. The course of vascular complications is summarized in table 4. No improvement in renal function, as measured by the 15-minute excretion of intravenously administered phenolsulfonphthalein was observed. Most of these patients had an initial 15-minute excretion of better than 20 per cent. There was no evidence of progressive renal damage during administration of the drug. No patients were observed to have a reduction in heart size as indicated by decrease in frontal surface area of 30 per cent or more plus a decrease in transverse cardiac diameter of more than 3 cm. from the predrug orthodiagram measurement. Only four patients were observed to have improvement in retinopathy* according to Keith and Wagener's classification.[14, 15] Three of these patients were in the

TABLE 4.—*Number of Patients in Each Smithwick Group Having a Reduction in Blood Pressure and Improvement in Vascular Complications after Receiving Apresoline for One Year or More (See Text for Discussion)*

Smithwick Classification	Number of Patients	Blood Pressure Reduced	Improved Vascular Complications
I	9	8	3
II	17	7	1
III	7	4	1
IV	7	1	2

Smithwick groups I and II classification, and one was in group III. The changes in this small group of patients are to be contrasted with the unchanged eyegrounds of 30 patients. It is of interest that six patients showed advancing retinopathy during this period of observation.

In the electrocardiogram of three patients, inverted T waves became upright or S-T segment displacement reverted to the isoelectric line.

Three women, all over age 45, in this group of 40, had initial slight nitrogen retention (20 to 30 mg. per 100 cc.) and all are still living with essentially the same degree of azotemia after one year of Apresoline therapy.

Tolerance. In our experience the hypotensive response to oral Apresoline appeared to persist

*These examinations were made by Dr. George S. Tyner, Department of Ophthalmology, Hospital of the University of Pennsylvania.

for as long as the drug was continued. A rise in pressure during treatment was usually corrected by an increase in dosage. Contrarily, several patients have required a reduction in maintenance dosage. (See fig. 2.)

Side Reactions. Usually side effects appeared just after the initiation of therapy and subsided within a week or two. Tachycardia was invariably produced. In some cases where headache was particularly bothersome, Pyribenzamine or Benadryl was prescribed with the Apresoline and afforded relief.[16] The symptoms reported by the 40 patients were (table 5): headache, 15 cases; tachycardia and palpitation, seven cases; nausea and vomiting, five cases; and urticaria, cutaneous flushing and lacrimation, one case each. Sixteen patients have been unable to tolerate Apresoline for as long as one week. Severe headache and palpitation accompanying the tachycardia were the most frequent reasons for discontinuing its use. Recently we have encountered less difficulty when using a lower initial dosage of 12.5 mg. four times daily for the first 10 to 14 days.

Toxicity. Prolonged administration of Apresoline has not produced toxic reactions attributable to a cumulative effect. No attempt was made to determine any specific effect of the drug on blood cell morphology or liver function.

Mortality during Therapy. The only death observed in this group was that of a 59 year old white man with symptoms of mild angina who had been on Apresoline for 12 months. This patient had grade III retinopathy, slight cardiac enlargement, and electrocardiogram showing slight changes characteristic of the hypertensive state, blood urea nitrogen of 14 mg. per 100 cc. with 30 per cent phenolsulfonphthalein excreted in 15 minutes. Thus, the patient was in Smithwick group III. The initial blood pressure while hospitalized was 200/130 and on a dosage of 50 mg. three times each day this pressure decreased to the range of 180/105 as an outpatient. Each attempt to increase the dosage beyond this led to headache. The patient was placed on a placebo and an increase of pressure was observed. Shortly after resuming Apresoline therapy, he developed a clinical picture suggesting coronary thrombosis and died. Postmortem examination was not made. It is our impression that this was a coincidence rather than a result of therapy by contrast with some of the deaths discussed in Grimson's report.[13]

TABLE 5.—*Numbers Who Reported Unpleasant Reactions in This Study of 40 Patients*

Headache	15	38%
Palpitation	7	18%
Nausea and Vomiting	5	12%
Urticaria	1	2%
Flushing	1	2%
Lacrimation	1	2%

COMMENT

We have not observed progressive vascular damage among the 33 patients in groups I, II and III (Smithwick) while on the program of oral Apresoline. Fifty-seven per cent of the patients in these groups have had a satisfactory reduction in blood pressure. In five of these patients there has been an improvement in the vascular complications noted before drug treatment was initiated. The fact that about 25 per cent of all patients started on this drug have remained on it for at least a year suggests that these patients were not seriously disturbed by the unpleasant aspects of this therapeutic program.

Our present impression is that the patient with minimal evidence of progression in vascular complications may be given oral Apresoline and a low salt intake so long as there is no evidence indicating further progression of damage. If clinical and laboratory data indicate increasing damage, and particularly if renal function measurements suggest further deterioration, we believe these signs warrant more drastic steps in treatment, with a trial of other potent experimental drugs.[4, 13, 17] Surgical intervention[18-20] is to be considered if these are likewise unsuccessful.

What we most need to know is: (a) Does Apresoline or any other depressor drug keep mild hypertensives from getting worse and thus obviate surgical intervention? (b) Does Apresoline prolong the lives of those with severe hypertension whose azotemia precludes

operation? It is obvious that a longer period of observation in a larger series of patients is needed before these questions can be answered.[21]

Summary

1. Oral Apresoline was an effective depressor agent in 57 per cent of hypertensive patients having a relatively good prognosis for survival, who took the drug for at least one year.

2. Among seven patients having the poorest survival prediction, only one individual had a reduction in blood pressure considered to be favorable.

3. The period of observation of the present study was too short to indicate whether or not Apresoline has favorably affected the natural history of hypertensive vascular disease.

4. We suggest that patients with severe essential hypertension, having good renal, cardiac and retinal findings, are suitable candidates for a trial of oral Apresoline. This agent may be continued so long as there is no evidence of progression as determined by periodic re-evaluation.

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Sumario Español

Pacientes con hipertensión esencial severa han sido cuidadosamente estudiados periódicamente en un esfuerzo para agruparlos de acuerdo a la expectativa de duración de vida. Cuarenta casos han sido observados en un regimen de Apresoline oral y dieta baja en sal. Diez y nueve de los 33 en el grupo con un pronóstico de vida relativamente bueno han tenido alguna diminución en la presión diastólica. Solamente uno de siete pacientes en el grupo correspondiente a Smithwick grupo IV ha tenido una reducción satisfactoria en presión arterial.

REFERENCES

[1] Smithwick, R. H.: The effect of sympathectomy upon the mortality and survival rates of patients with hypertensive cardiovascular disease. In Bell, E. T.: Hypertension. Minneapolis, University of Minnesota Press, 1951. P. 492.

[2] Evelyn, K. A., Alexander, F., and Cooper, S. R.: Effect of sympathectomy on blood pressure in hypertension. J. A. M. A. **140:** 592, 1949.

[3] Palmer, R. S., Loufbourow, D., and Doering, C. R.: Prognosis in essential hypertension: Eight year follow-up study of 430 patients on conventional medical treatment. New England J. Med. **239:** 990, 1948.

[4] Hafkenschiel, J. H.: Newer drugs in treatment of hypertension. In Advances in Medicine and Surgery from the Graduate School of Medicine of the University of Pennsylvania, Philadelphia, Saunders, 1952. P. 136.

[5] —: Recent advances in the treatment of severe hypertension. Pennsylvania M. J. **55:** 120, 1952.

[6] Gross, F., Druey, J., and Meier, R.: A new group of depressor substances with a special type of effect. Experientia **6:** 19, 1950.

[7] Reubi, F. C.: Renal hyperemia induced in man by a new phthalazine derivative. Proc. Soc. Exper. Biol. & Med. **73:** 120, 1950.

[8] Freis, E. D., and Finnerty, F. A., Jr.: Suppression of vasomotor reflexes in man following 1-hydrazinophthalazine (C 5968). Proc. Soc. Exper. Biol. & Med. **75:** 23, 1950.

[9] Clark, J. K., and Crosley, A. P., Jr.: Unpublished data.

[10] Hafkenschiel, J. H., Friedland, C. K., Yobbagy, J., and Crumpton, C. W.: The effects of 1-hydrazinophthalazine (C 5968) on cerebral hemodynamics and oxygen metabolism in hypertensive subjects. J. Pharmacol. & Exper. Therap. **103:** 345, 1951.

[11] Jeffers, W. A.: Evaluation of the patient with hypertension. In Advances in Medicine and Surgery from the Graduate School of Medicine of the University of Pennsylvania, Philadelphia, Saunders, 1952. P. 130.

[12] —, Sheiman, S. C., and O'Brasky, G. H.: Use of a simple postural test in neurocirculatory asthenia. Am. J. M. Sc. **210:** 511, 1945.

[13] Grimson, K. S., Orgain, E. S., Rowe, C. R., and Sieber, H. A.: Caution with regard to use of hexamethonium and Apresoline. J. A. M. A. **149:** 215, 1952.

[14] Wagener, H. P., and Keith, N. M.: Diffuse arteriolar disease and hypertension and associated retinal lesions. Medicine **18:** 317, 1939.

[15] Leopold, I. H., Kety, S. S., Jeffers, W. A., Hafkenschiel, J. H., and Shenkin, H. A.: Correlation of the cerebrovascular resistance and the grade of hypertensive retinal findings. Am. J. Ophth. **32:** 365, 1949.

[16] Schroeder, H. A.: The effect of 1-hydrazinophthalazine in hypertension. Circulation **5:** 28, 1952.

[17] —: Control of hypertension by hexamethonium

and 1-hydrazinophthalazine: Preliminary observations. Arch. Int. Med. **89:** 523, 1952.

[18] ZINTEL, H. A.: Sympathectomy. In Advances in Medicine and Surgery from the Graduate School of Medicine of the University of Pennsylvania. Philadelphia, Saunders, 1952. P. 160.

[19] —, WOLFERTH, C. C., JEFFERS, W. A., HAFKENSCHIEL, J. H., AND LUKENS, F. D. W.: Ninety-five per cent subtotal adrenalectomy for essential hypertension. In Surgical Forum. Philadelphia, Saunders, 1951. P. 556.

[20] WOLFERTH, C. C.: Adrenalectomy in relation to hypertension. Tr. & Stud. Coll. Physicians, Philadelphia **19:** 135, 1952.

[21] PERERA, G. A.: The natural history of hypertensive vascular disease. In BELL, E. T.: Hypertension. Minneapolis, University of Minnesota Press, 1951. P. 369.

Observations on the Carotid Sinus Reflex and Angina Pectoris

By A. Stone Freedberg M.D., and Joseph E. F. Riseman, M.D.

The effect of carotid sinus pressure on the duration and character of attacks of angina pectoris induced by exercise under controlled conditions has been studied in 13 patients. Observations are presented which are consistent with the hypothesis that stimulation of the carotid sinus induces relief of cardiac pain by interruption of sympathetic reflex arcs or sensory pathways. The usefulness of carotid sinus pressure as a diagnostic test and a therapeutic measure in angina pectoris is discussed.

IN PREVIOUS studies[1] data were presented in support of the concept that coronary artery vasomotor changes, reflex in origin, exerted a contributory influence in the precipitation of attacks of angina pectoris. The influence of reflexes mediated through the vagus nerve in precipitating attacks of angina pectoris has been the subject of few studies. It has been observed[2–10] that stimulation of the carotid sinus relieves the pain of angina pectoris. We have not been able to find any studies on the mechanism of relief of cardiac pain by carotid sinus stimulation. The purpose of this communication is to report our studies on the mechanism of the relief of cardiac pain induced by carotid sinus stimulation. The effect of carotid sinus pressure on the exercise tolerance of patients with angina pectoris is also reported.

Materials and Methods of Study

In most of the published reports of the beneficial effect of carotid sinus pressure in angina pectoris, the anginal attacks were spontaneous and the usual duration of pain unknown. In the studies of Wayne and Laplace,[8] although anginal attacks were induced by exertion, the amount of exercise necessary to produce pain was variable from experiment to experiment. The importance of carefully standardized conditions, especially cold, in studying the precipitation and the duration of attacks of angina pectoris in the laboratory has been previously demonstrated.[11, 12] Accordingly for the present study subjects were selected who had been observed at weekly intervals for many months to years in a special clinic for the study of angina pectoris. Thus their clinical course was well known, the response to exercise and to various therapies was repeatedly observed and the actual duration of attacks induced by exercise had been repeatedly measured and found to be reproducible.

In our previous studies[13, 13a, 13b] the response to nitroglycerin was used to determine the likelihood of response to other forms of treatment and served to divide patients into three groups: Group I patients (tables 1, 2, 3 and 4) are "marked reactors" to nitroglycerin. Two minutes after the sublingual administration of 0.3 mg. of nitroglycerin these patients are able to perform approximately 100 per cent or more work than had been possible without medication. This increase in exercise tolerance in group I patients is accompanied by a marked decrease in the RS-T deviations consequent to exercise. Patients in group II, termed "moderate reactors," are able to do approximately 50 per cent more work two minutes after the sublingual administration of 0.3 mg. of nitroglycerin. Patients in group III, termed "nonreactors," show no response to the administration of nitroglycerin.

All tests were carried out at least one hour after a light breakfast and after the patient had rested a minimum of one-half hour after coming to the laboratory. Only one test was carried out on any one day. The patient received no medication during the carotid sinus experiments.

After the amount of exercise necessary to induce angina and the duration and characteristics of pain had been measured on numerous occasions (10 to 50) the effect of carotid sinus pressure on the duration of pain was measured in the following fashion. Immediately after the patient stopped exercise because of pain he seated himself on the two-step staircase; one observer, who was stationed behind the patient, then located as quickly as possible the right or left carotid sinus region and stimulated it by pressure and massage. The time necessary to locate the carotid sinus, the duration of stimulation and the duration as well as the character of

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pain was measured by another observer with the aid of a stop watch. In measuring the duration of anginal pain, all tests in which carotid sinus stimulation induced syncope were necessarily excluded. Uniform stimulation of the carotid sinus was attempted; involuntary stiffening of the sternocleidomastoid muscles (usually in later experiments) made accurate location and control of severity of pressure difficult to obtain.

As a control of the carotid sinus experiments, in other experiments with the onset of cardiac pain the patient was seated and pressure was exerted on the right or left sternocleidomastoid muscle. The latter procedure was without effect on the duration or character of the anginal attack.

I. Effect of the Carotid Sinus Pressure on the Duration of the Pain of Angina Pectoris

The effect of carotid sinus pressure on the duration and characteristics of anginal pain was studied in 13 patients (table 1). In most instances three to seven seconds elapsed before the carotid sinus could be located. The usual duration of stimulation was approximately six seconds with extremes of 3 to 40 seconds. In all 13 patients some relief of pain was observed as a consequence of carotid sinus stimulation. In 11 of the 13 patients the onset of relief of pain occurred during or within a few seconds after carotid sinus stimulation. In four of five patients (cases 7, 10, 11, 12, and 13) with attacks of one to four minutes duration, carotid sinus pressure induced temporary relief of anginal pain, persisting for 22 to 64 seconds (table 1). In each of these four patients pain of unaltered intensity, compared with precarotid sinus pressure, recurred and the total duration of the attack was not appreciably altered from that observed in control experiments. In the fifth patient (case 12) the usual duration of pain was 180 seconds; following carotid sinus stimulation intermittently for 40 seconds, pain disappeared and did not return. In one instance (case 4) anginal pain disappeared from the right side of the chest during right carotid sinus pressure while persisting on the left side, while in case 7 anginal pain disappeared from the chest during carotid sinus pressure while persisting in the shoulder. In two patients (cases 2 and 10) relief of pain was not uniformly induced by carotid sinus stimulation from experiment to experiment. In one of these, case 2, and similarly in cases 3 and 6, carotid sinus stimulation of one side was effective while pressure on the other side had no, or less, effect on cardiac pain. In two other patients (cases 5 and 8) right or left sided stimulation was similarly effective in relieving cardiac pain. In no instance was prolongation of anginal pain induced by carotid sinus stimulation.

Studies on the Mechanism of Relief of Pain

A. Effect of Carotid Sinus Pressure in Patients with Angina Pectoris as Compared with Patients in the Same Age Group without Angina Pectoris

Fifteen patients with angina pectoris of arteriosclerotic etiology and 50 patients of the same age group without angina pectoris were studied. None of the patients in either group had ever suffered a spontaneous episode of syncope or had a history suggesting a hyperactive carotid sinus syndrome. The patients were seated and connected to an electrocardiograph machine. Using lead V_{4R}, with the camera running continuously, right carotid sinus pressure was applied for six seconds. Calculations of the cardiac rate changes were made from the electrocardiographic tracings. The degree and severity of carotid sinus pressure was felt to be the same in both groups. The blood pressure was measured by the auscultatory method.

Results. In 25 of the 50 patients in the control group, right carotid sinus pressure for six seconds induced no discernible change in cardiac rate or blood pressure and was unattended by symptoms. A similar lack of response to carotid sinus pressure was observed in 3 of the 15 patients with angina pectoris (table 1, cases 1, 12 and 13). The incidence of asystole and auriculoventricular block was the same in both groups. The duration of the induced asystole in the patients with angina pectoris averaged six seconds as compared with three seconds in the control group. Syncope and convulsions were observed in 5 of the 15 angina pectoris patients and in 2 of the 50 control patients.

Further Evidence of the Increased Sensitivity of the Carotid Sinus Reflex in Angina Pectoris.

TABLE 1.—*The Effect of Carotid Sinus Stimulation on the Duration of Attacks of Angina Pectoris*

Untreated Control Attacks		Attacks Treated by Carotid Sinus Stimulation					
Case No.	Usual Duration of Pains (seconds)	Carotid Sinus Stimulation	Time from End of Exercise to Start of C.S. Pressure (seconds)	Time from End of Exercise to End of C.S. Pressure (seconds)	Time of First Disappearance of Pain (seconds)	Time of End of Attack (seconds)	Comment
				Group I			
1. H. B.	18	Right	4	7	7	7	Attack shortened.
2. S. E.	27	Right	3.5	10.5	10	10	Attack shortened.
		Left	3	11	30	30	No change.
3. S. L.	30	Right	2	4	4	4–6	Attack shortened.
		Left	?	6	6	22	Pain disappeared during carotid sinus pressure; returned 15 seconds after exercise.
4. N. S.	30	Right	3	18	15	30	At 15 seconds pain disappeared on right side of chest; pain on left side persisted for 15 seconds.
		Right	2	8	32	32	No change.
5. M. L.	45	Right	7	20	20	20	Pain disappeared during carotid sinus stimulation.
		Left	?	18	30	30	Attack shortened.
6. R. S.	58	Right	5	13	55	55	No change.
		Left	?	6	32	32	Attack shortened.
7. S. R.	250	Right	2.6	8.2	8.2	200	Pain disappeared from chest during carotid sinus pressure, but persisted unchanged in left shoulder. Pain returned in chest 28 seconds after exercise.
		Right	3	14	24	212	Pain disappeared from chest 7 seconds after carotid sinus stimulation ended; pain persisted in shoulder. Pain in chest returned 41 seconds after exercise.
				Group II			
8. P. R.	27	Right	5	10	10	10	Pain disappeared during carotid sinus pressure.
		Left	3	10	10	10	Pain disappeared during carotid sinus pressure.
9. B. K.	55	Right	?	6	39	39	Attack shortened.
				Group III			
10. H. Y.	62	Right	2.5	8	8	58	Pain disappeared during carotid sinus pressure; pain returned 22 seconds after exercise. Total duration of pain unchanged by carotid sinus pressure.
		Right	2	8	60	60	No change.
11. J. M.	125	Right	7	12	12	116	Chest pain and wheezing disappeared during carotid sinus pressure. Chest pain returned 31 sec. after exercise. Total duration of pain unchanged by carotid sinus pressure.
12. N. B.	180	Right	?	Intermittent to 40 sec.	40	40	Attack shortened.
13. H. M.	250	Right	7	16	17	268	Pain disappeared during carotid sinus pressure; pain returned 40 seconds after exercise. Total duration unchanged.
		Right	2	11	11	255	Pain disappeared during carotid sinus pressure; pain returned 64 seconds after exercise. Total duration unchanged.

The results presented above suggested that the carotid sinus reflex was more sensitive in patients with angina pectoris than in patients of the same age group who did not have angina pectoris. The opportunity arose to make studies of carotid sinus sensitivity in a patient with angina pectoris during a period when the patient was having many attacks of angina pectoris daily as well as during a prolonged period of remission from angina pectoris lasting many weeks.

In these studies the patient was seated and connected to the electrocardiographic machine. With the camera running continuously lead V_{4R} was taken and right carotid sinus stimulated. The duration of stimulation was measured from electrocardiograms by marking the onset and offset of carotid sinus pressure. In varying the duration of stimulation from 1 to 10 seconds we attempted to keep the severity of pressure uniform in all experiments. Only one experiment was carried out on each day. The duration of the induced asystole was measured from the electrocardiographic tracings.

The effect of stimulation of the right carotid sinus was more marked when the patient was having many anginal attacks than during a remission from his angina (fig. 1). During the remission from angina, up to 10 seconds, right carotid sinus pressure produced a maximum asystole of 6.5 seconds. Faintness, syncope or convulsions were not observed. During the period when the patient was suffering two to three daily attacks of angina, pressure on the carotid sinus for two seconds induced an asystole of six and one-half seconds and pressure for five to six seconds produced an asystole of $8\frac{1}{2}$ to 10 seconds and in both instances syncope and convulsions were observed (fig. 1). The patient was immediately laid down in each of these latter episodes. Recovery was prompt and sequelae were absent.

B. Relationship of Relief of Pain by Carotid Sinus Stimulation to Changes in Cardiac Rate

In previous studies[2-9] the beneficial effects of carotid sinus stimulation in the relief of cardiac pain have been ascribed to cardiac slowing; the latter has been estimated by auscultation.

In our studies, the changes in pulse rate were calculated from electrocardiographic tracings. Standard electrodes were adjusted and affixed to both arms below the insertion of the deltoid muscle and also to the precordium over the cardiac apex. With the patient standing at rest, prepared to exercise, a 15 second tracing of lead V_{4R} was obtained. The standard exercise test was performed as usual with the electrodes in place and the electrocardiographic machine (but not the camera) running continuously. The camera was started before the predicted

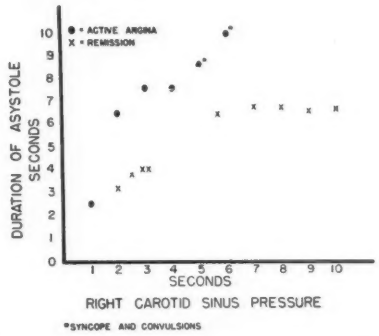

FIG. 1. Effect of carotid sinus pressure tests in H. St. demonstrating a marked increase in sensitivity during a period of days when the patient was experiencing many attacks of angina pectoris. (See text for description.) Dots indicate tests when patient was having frequent attacks; crosses indicate tests when patient was free of attacks.

cessation of exercise and tracings (at least 15 seconds in duration) were obtained at the onset of cardiac pain and the cessation of exercise and usually one, two, three and five minutes thereafter. The onset and offset of carotid sinus pressure was indicated on the tracing. The cardiac rate (beats per minute) was calculated for each cycle from the formula

$$\frac{60}{\text{R-R in seconds}}$$

1. Relief of Cardiac Pain by Carotid Sinus Stimulation Not Associated with Cardiac Slowing. In 10 of 13 patients studied (table 1) some degree of slowing was obtained by carotid sinus stimulation. In three patients (table 1, cases 1, 12 and 13) relief of cardiac pain by carotid sinus stimulation was obtained without slowing of the heart rate. In patient H. B.,

following pressure on the right carotid sinus for three seconds, the attack of pain ended; the attack was shortened from a usual duration of 18 seconds to 7 seconds. The heart rate was unchanged during the period of carotid sinus stimulation. In patient N. B. intermittent stimulation of the right carotid sinus was carried out for 40 seconds, at which time cardiac pain disappeared. The duration of the usual attack of angina pectoris in this patient was 180 seconds. In this patient, carotid sinus stimulation was without effect on the cardiac rate. Similarly in patient H. M., relief of cardiac pain for approximately one minute was obtained following stimulation of the right carotid sinus, although carotid sinus stimulation was not associated with any change in cardiac rate.

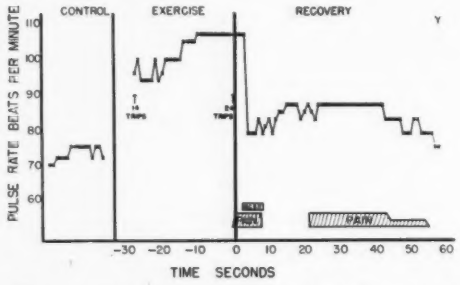

FIG. 2. The effect of carotid sinus pressure on heart rate and anginal pain in H. Y. (See text for description.)

II. The Lack of Relationship between the Degree of Cardiac Slowing and Relief of Cardiac Pain. This is exemplified by the observations made in patient H. Y. (figs. 2 and 3). Pressure on the right carotid sinus (fig. 2) was begun two and seven-tenths seconds after the onset of cardiac pain and continued for five and one tenth seconds. The cardiac rate fell from 105 to 80. During the period of carotid sinus stimulation cardiac pain disappeared and did not return for 16 seconds. The total duration of the attack was 55 seconds. In the same patient on a different day the onset of cardiac pain began after the same number of trips on the staircase (fig. 3). Stimulation of the right carotid sinus was begun three seconds after the onset of pain and continued for six and one-half seconds. The cardiac rate fell from 128 to 85, a more marked decrease in cardiac rate than was observed in the experiment illustrated in figure 2. Cardiac pain was unaffected.

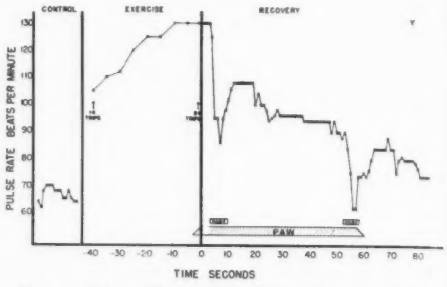

FIG. 3. The effect of carotid sinus pressure on heart rate in H. Y. showing marked cardiac slowing and no effect on anginal pain. The termination of cardiac pain after the second carotid sinus pressure was completed was coincidental with the decrease in cardiac rate. The usual duration of cardiac pain in this patient was 55 to 60 seconds. (See figure 3.)

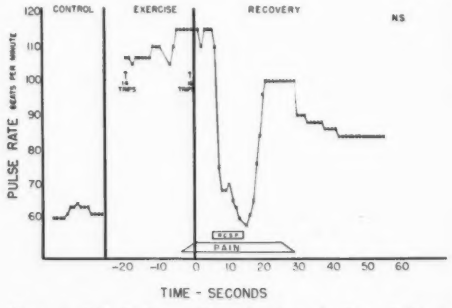

FIG. 4. Marked cardiac slowing during right carotid sinus pressure in N. S. and no effect on the duration of the attack of angina pectoris induced by exercise. In other attacks in this patient temporary relief of cardiac pain occurred with carotid sinus pressure.

III. Marked Slowing of Cardiac Rate during Carotid Sinus Stimulation without Effect on Cardiac Pain. In patient N. S. cardiac pain began after 18 trips on the staircase (fig. 4). Stimulation of the right carotid sinus was begun five seconds after the end of exercise and continued for nine seconds. The cardiac rate fell from 115 to 56; the rate was below 80 for approximately half the duration of the attack of pain. The attack of angina pectoris continued unaltered and the total duration of pain was

unaltered as compared with the duration of induced but untreated attacks (fig. 5) during which the heart rate was over 100 beats per minute.

IV. The Occurrence of the Relief of the Pain of Angina Pectoris Following Carotid Sinus Pressure after the Cardiac Rate Has Returned to the Control Level. In patient P. R. during the stimulation of the right carotid sinus the heart rate slowed initially from 107 to 73, but promptly rose to 107, although stimulation was continued. Cardiac pain disappeared coincident with the end of carotid sinus pressure and at a time when the heart rate had returned to the precarotid sinus stimulation rate. The

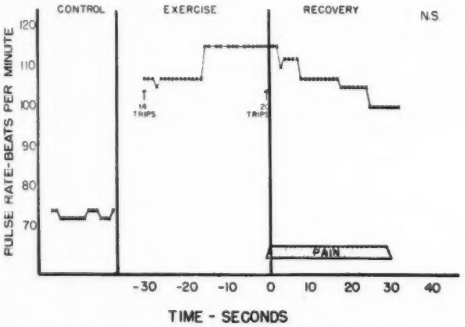

FIG. 5. Heart rate before, during and after exercise and the duration of an attack of angina pectoris in N. S. (Compare with figure 4.)

total duration of cardiac pain was 10 seconds, considerably shorter than the usual duration of control attacks (table 1).

A somewhat similar sequence was observed in patient S. R. (fig. 6); right carotid sinus pressure was begun approximately three seconds after the onset of chest pain and continued for 14 seconds. Eight seconds after stimulation was begun the cardiac rate abruptly fell from 115 to 73; chest pain continued undiminished. It is possible that actual stimulation of the sinus did not begin until seven to eight seconds after the onset of cardiac pain. Seven seconds after carotid sinus pressure was discontinued, chest pain disappeared for a period of 17 seconds (fig. 6). The cardiac rate at the onset of relief of pain was 115. It should be emphasized that although anginal pain disappeared from the chest during this period of time, shoulder pain continued undiminished. The total duration of the attack of angina pectoris was 212 seconds (the usual duration was 250 seconds).

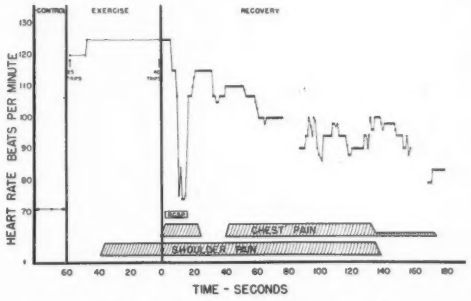

FIG. 6. The heart rate and effect of right carotid sinus pressure in S. R. The relief of cardiac pain occurred after the heart rate had returned to the same rate recorded before carotid sinus pressure. (See text for description.)

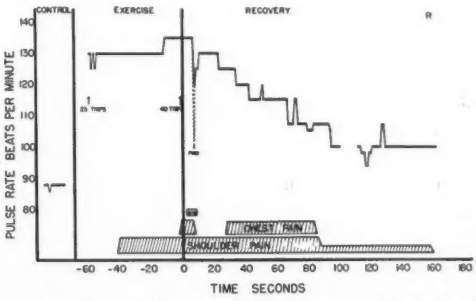

FIG. 7. Another experiment showing the lack of relationship between cardiac rate and relief of cardiac pain following carotid sinus pressure in S. R. (Compare with figure 6.)

In the same patient, S. R., on a different occasion, (fig. 7) right carotid sinus pressure was begun two and six-tenths seconds after the patient stopped exercise, and continued for five and six-tenths seconds. The cardiac rate momentarily slowed from 135 to 98, returning within one and five-tenths seconds to 120 at the end of carotid sinus stimulation, rising to 130 a few seconds later. Pain disappeared from the chest, while persisting in the shoulder, at the end of carotid sinus stimulation during a period when the cardiac rate was only slightly below the precarotid sinus pressure level. The

duration of relief of pain was approximately 22 seconds. The total duration of the attack of angina pectoris was 200 seconds (the usual duration 250 seconds, table 1).

C. The Effect of Carotid Sinus Stimulation on the Exercise Tolerance of Patients with Angina Pectoris: With a Comparison of the Effect of Nitroglycerin on the Exercise Tolerance of the Same Patients

The available evidence from animal experimentation concerning the influence of the vagus nerve on coronary blood flow is conflicting.[14, 15] Some observers, however, believe that the vagus nerve is vasodilator to the coronary arteries. It was hoped that some light might be cast on this subject by determining the effect of vagal stimulation on the exercise tolerance of patients with angina pectoris and comparing the results with those obtained after the use of a coronary vasodilator such as nitroglycerin. These studies seemed particularly appropriate since it was possible that the effect of carotid sinus stimulation in relieving the pain of angina pectoris might be due to coronary vasodilation.

The effect of carotid sinus pressure on the exercise tolerance was studied in 10 patients with angina pectoris (table 2). The exercise tolerance tests were performed under the usual standardized conditions except that immediately prior to exercise the right carotid sinus was stimulated for six seconds. The severity of pressure was, of necessity, mild since the stimulation was done with the patient erect. On another day, pressure of approximately the same severity and duration was exerted on the right sternocleidomastoid muscle immediately before exercise. The experiments in which the right carotid sinus was stimulated were performed on at least two occasions in each patient.

Results. After right carotid sinus stimulation five patients were able to perform at least 50 per cent more work before developing pain as compared with control exercise tolerance tests. The response to carotid sinus pressure was independent of the response of the patient to nitroglycerin; a marked increase in exercise tolerance was obtained following carotid sinus stimulation in some patients who did not respond to nitroglycerin, for example, patient H. M. (table 2), while little effect was observed after stimulation in some patients who showed a marked response to nitroglycerin, for example, patients M. L., and N. S. (table 2). In one, H. M., of the two patients in group III who did not respond to nitroglycerin, a 100

TABLE 2.—*The Effect of Carotid Sinus Pressure on the Ability to Work*

Case	Control Exercise Tolerance Tests. No Medication. Pressure on Sternocleidomastoid Muscle	Pressure on Carotid Sinus Immediately before Exercise	
	Trips	Trips	Per cent Increase
Group I			
HS	24	36	+50
SR	40	58	+45
HB	75	100*	+33*
NS	24	30	+25
ML	36	42	+16
RS	20	X	
Group II			
LW	40	74	+85
PR	45	74*	+65*
BK	30	23	−23
Goup III			
HM	20	41	+105
BA	40	40	0

* No attack. Stopped because of fatigue.
X Exercise not attempted because of faintness.

per cent increase in exercise tolerance was demonstrated after carotid sinus pressure. On the other hand, of the five patients in group I, carotid sinus pressure resulted in an increased exercise tolerance of 50 per cent in one patient, approximately 50 per cent in another and less than 25 per cent in the remaining three. In each of these five patients the prophylactic administration of nitroglycerin induced an increase in exercise tolerance of at least 100 per cent.

Electrocardiographic Studies. We have previously shown (13) that the administration

of nitroglycerin to patients with angina pectoris not only results in an increased ability to perform work before the development of pain, but also prevents the S-T segment and T wave changes which are consequent to exertion.

In two patients with angina pectoris (H. B. and P. R.) electrocardiograms were obtained in the manner described above after a fixed exertion insufficient to produce pain, namely 10 to 15 trips. The changes in the RS-T segments and T waves were measured in at least 10 consecutive complexes and the results averaged.

Pressure on the carotid sinus before exertion did not prevent the RS-T segment and T wave changes consequent to exertion.

The Effect on the Exercise Tolerance of a Group of Vagomimetic, Vagolytic and Antispasmodic Drugs. The increase in exercise tolerance consequent to carotid sinus stimulation in some patients suggested the possibility that vagomimetic substances such as physostigmine salicylate might have a beneficial effect in patients with angina pectoris. It also seemed appropriate to study these and vagolytic substances in the hope that some light might be thrown on the role of the vagus on the coronary circulation.

The administration of 1.3 mg. of physostigmine salicylate four times daily, the last dose being taken two hours before the performance of the exercise tolerance test, was followed by an increase in exercise tolerance in 2 (H. B. and H. St., table 3) of 11 patients with angina pectoris studied. It may be noted that an increase in exercise tolerance of similar magni-

TABLE 3.—*The Effect of the Oral Administration of Physostigmine Salicylate (1.3 mg. q.i.d.) on the Ability to Work*

Case	No Medication	After Physostigmine	
	Trips	Trips	Per cent Increase
Group I			
HSt	40	66	+65
HB	75	118	+58
SE	25	32	+28
NS	30	36	+20
RS	20	22	+10
ML	44	42	−5
SR	34	29	−15
Group II			
LW	40	45	+12
SL	30	26	−13
SW	40	30	−25
Group III			
BA	40	31	−23

TABLE 4.—*The Effect of the Oral Administration of Atropine Sulfate (0.5 mg. q.i.d.) on the Ability to Work*

Case	Without Medication	After Atropine Sulfate	
	Trips	Trips	Per cent increase
Group I			
SR	34	75	+127
H. Shr	25	35	+40
H. Shl	40	40	0
RS	20	20	0
YE	20	19	−5
EA	60	55	−8
EW	40	30	−25
Group II			
JM	40	60*	+50*
PR	30	38	+27
LW	40	40	0
BS	25	25	0
BL	10	10	0
BK	20	18	−10
IF	35	27	−24
JG	29	19	−34
Group III			
AR	25	33	+32
CH	13	16	+22
AS	24	26	+8
H. Bk	40	42	+5
J. Go	60	61	+2
LS	21	21	0
DC	35	32	−5
JL	35	30	−14
RK	38	32	−15
H. Ch	32	26	−19
ES	25	20	−20

* No attack. Stopped because of fatigue.

tude was obtained in these two patients following carotid sinus pressure (table 2). The increase in exercise tolerance, however, did not equal that observed after the administration of nitroglycerin.

The administration of prostigmine bromide, 15 mg. four times daily, to five patients was not associated with an increased exercise tolerance.

The effect on the exercise tolerance of the administration of 0.5 mg. of atropine sulfate four times daily was studied in 26 patients with angina pectoris (table 4). An increase in exercise tolerance from 40 to 125 per cent was demonstrated in only three patients.

The antispasmodic drugs, Syntropan and Novatropine, were studied in 8 and 10 patients respectively. The administration of 100 mg. Syntropan and 10 mg. Novatropine (two tablets) four times daily was without effect on the exercise tolerance.

Comment

It is clear from these studies that stimulation of the carotid sinus may abolish temporarily or completely the pain of an induced attack of angina pectoris. Various considerations discussed below are in agreement with the following hypothesis which is proposed as the mechanism of the induced relief of cardiac pain by carotid sinus stimulation. Stimulation of the carotid sinus induces the relief of cardiac pain by interruption of reflex arcs; the relief is neurogenic in origin and is not related to a change in the myocardium induced by carotid sinus pressure.

The recurrence of pain following a period of relief as a consequence of carotid sinus pressure in those patients whose attacks ordinarily lasted longer than a minute with a total duration similar to untreated attacks would indicate that no significant change had occurred in the discrepancy between myocardial demand and blood supply as a consequence of carotid sinus stimulation. The fact that stimulation of the carotid sinus caused relief of pain in the right side of the chest (patient N. S.) while pain persisted in the left side and the disappearance of chest pain (S. R.) while pain persisted in the shoulder indicates a neurogenic effect on the afferent impulses mediating pain.

The disappearance of pain occurs within a few seconds; the speed of the relief of pain is in favor of a neurogenic mechanism. The previously mentioned disappearance of pain in certain areas while persisting in others, indicates alteration in sensory pathways. This is similar to the disappearance of pain following thyroidectomy[17] and nerve blocking procedures.[18] The relief of cardiac pain by interruption of sympathetic nerves has been well established. Interruption of nerve pathways in the skin,[19, 20] cervical ganglionectomy,[21] and injection of various sympathetic nerves in the cervical and thoracic region are also associated with relief of cardiac pain.[22]

The relationship of the carotid sinus to the sympathetic nervous system has been clearly demonstrated by Heymans and associates.[23] Together with stimulation of the vagus nerve, there is a simultaneous inhibition of the sympathetic nervous system. Bronk and his coworkers[26] showed that during carotid sinus stimulation there was a decreased number and strength of action potentials as recorded from the cervical sympathetic fiber to the carotid sinus.

Ferris, Capp and Weiss[25] postulated that the effect of carotid sinus pressure in inducing syncope was, in some instances, due to stimulation of a cerebral center. In our studies, the patients were able to perceive the pain of a needle while obtaining relief of cardiac pain during carotid sinus stimulation. Instances where a changed sensorium or syncope consequent to carotid sinus stimulation were observed have been excluded. We cannot, however, deny the possibility of an effect on some cerebral center.

Our studies yield no evidence that carotid sinus stimulation induces coronary artery vasodilatation. No relationship was observed between the increase in exercise tolerance after stimulation, and that observed after the administration of vasodilators (table 2). An increased exercise tolerance was observed after stimulation in patients, in whom nitroglycerin was without effect, and vice versa. Furthermore, pressure upon the carotid sinus before exercise, while associated with an increased exercise tolerance, did not prevent the RS-T segment changes consequent to exertion. In

previous studies[13] we have shown that the increased exercise tolerance following the administration of nitroglycerin is accompanied by a decrease or absence of the RS-T segment changes consequent to exercise.

An additional consideration against the occurrence of vasodilation as a causative factor in the relief of cardiac pain by carotid sinus pressure is the speed of the reaction. Previous studies[12, 16] using various vasodilators have shown that relief of cardiac pain occurs in 20 to 30 seconds. The relief of pain associated with carotid sinus pressure occurred in almost all instances during or shortly after pressure the average duration of which was about six seconds. It would be expected that if vasodilation occurred with pressure on a carotid sinus a period would elapse during which cardiac anoxia was relieved by increased blood flow (similar to that observed after amyl or octyl nitrite) before relief or cardiac pain occurred; recurrence of pain of unaltered intensity and an unaltered duration of prolonged attacks would not be expected if significant coronary vasodilatation occurred.

On the basis of auscultatory findings previous authors have pointed out the association of cardiac slowing with the relief of pain by carotid sinus stimulation. It was to be expected, as has been demonstrated by many others, that stimulation would induce cardiac slowing in most subjects with coronary artery disease and angina pectoris. Our studies, however, show no relationship between the changes in cardiac rate following pressure on a carotid sinus and the relief of pain. Thus, marked cardiac slowing was obtained without relief of pain and relief of pain occurred when cardiac slowing was absent or not significant. Furthermore, in the same patient (H. Y.) in several attacks similar degrees of cardiac slowing were obtained during carotid sinus stimulation with relief of pain in one attack, and not in others.

The Usefulness of Carotid Sinus Pressure as a Diagnostic Test

It has been suggested by Sigler and others[6, 7, 26, 27] that the demonstrated increased sensitivity of the carotid sinus reflex in patients with coronary artery disease may be used as a diagnostic test. The studies of Mandelstamm and Lipshitz,[28] Weiss[29] and others indicate that the carotid sinus reflex is more active in the older age groups and particularly in the presence of coronary artery disease. Parry[30] was presumably the first to observe this phenomenon. Others, including Hering[31] and Prusick,[32] also pointed out the increased sensitivity of the carotid sinus reflex in patients with angina pectoris. Sigler[27] stated "the test may perhaps be considered to be a definite sign of coronary disease under the following condition; if it occurs as an independent phenomenon unassociated with other reflexes of the carotid sinus group such as a marked fall in blood pressure and cerebral manifestations including dizziness, sensory disturbances and syncope . . . and if it appears after comparatively slight pressure on the carotid sinus region and other vagal disturbances occur." Our own studies show that the effects of a definite degree of carotid sinus stimulation are more marked in patients with angina pectoris of arteriosclerotic etiology, than in patients of a similar age group without this condition. It should, however, be pointed out that some patients with angina pectoris of arteriosclerotic etiology do not have a sensitive carotid sinus.

It has been well established that the effects of carotid sinus stimulation are more marked in the older age groups than in the younger age groups. It is, however, incorrect to assume that coronary arteriosclerosis need occur with aging, nor is coronary arteriosclerosis synonymous with angina pectoris. Many patients with coronary arteriosclerosis and old coronary occlusions never suffer from angina pectoris.[33]

More recently Levine[34] has suggested that the relief of pain after pressure on the carotid sinus may be used as a diagnostic test for angina pectoris. At the present time it has not been demonstrated that the relief of pain following carotid sinus stimulation is specific for cardiac pain; in some patients, carotid sinus pressure has no effect on cardiac pain.[2, 3, 5] It should be emphasized, moreover, that the dangers of carotid sinus stimulation are real. Prusick and Herles[32] concluded that the carotid sinus pressure test may be a dangerous diag-

nostic test. They reported four cases where carotid sinus pressure produced asystole, syncope and convulsions and in one instance a fatal result. Similarly, one third of a small group of patients studied by us showed syncope and convulsions following six seconds of carotid sinus stimulation. The degree of sensitivity in one patient was such that two seconds of carotid sinus pressure produced an asystole of over six seconds. Downes[35] reported a series of surgical cases in which carotid sinus reflexes were implicated in the death of the patients. Askey[36] has reported the appearance of hemiplegia in seven patients after carotid sinus stimulation; other observations are confirmatory.[37, 38] Ventricular fibrillation[40] and complete heart block[41] have also been reported after carotid sinus stimulation.

The considerations pointed out above militate against the usefulness of carotid sinus pressure as a therapeutic agent. Mandelstamm[7] describes one patient, a female, aged 50, who obtained relief of angina pectoris by self pressure on the carotid sinus. Patients have, in instances of paroxysmal supraventricular tachycardia, been taught to stimulate their own carotid sinuses to abolish the attack.[42] In contrast to the observations in angina pectoris, syncope and convulsions following carotid sinus pressure under these circumstances are rare.

Summary and Conclusions

1. The effect of carotid sinus pressure on the duration and character of attacks of angina pectoris induced by exercise under controlled laboratory conditions has been studied in 13 patients. In all 13 patients some relief of cardiac pain was observed consequent to right or left carotid sinus stimulation. In 11 of the 13 patients, the onset of relief of cardiac pain occurred during or shortly after approximately six seconds of carotid sinus stimulation. In patients whose attacks of angina pectoris ordinarily lasted less than one minute, carotid sinus pressure terminated the attack. In four of five patients with attacks of one to four minutes duration, carotid sinus stimulation induced temporary relief of anginal pain persisting for 22 to 64 seconds; in each instance anginal pain returned in complete intensity and the total duration of the attack was not significantly altered in comparison to induced attacks not treated by carotid sinus pressure. In one patient, pain disappeared from the right side of the chest during right carotid sinus pressure while persisting on the left side, while in a second patient, pain disappeared from the chest during carotid sinus pressure, while persisting in the shoulder. These observations are consistent with the hypothesis that stimulation of the carotid sinus induces relief of cardiac pain by interruption of sympathetic reflex arcs or sensory pathways.

2. Various studies yielded no evidence that carotid sinus pressure relieves cardiac pain by inducing coronary artery vasodilation or by altering the discrepancy between myocardial demand and blood supply observed in the attack of angina pectoris. Carotid sinus pressure before exercise resulted in an increase in exercise tolerance in 5 of 10 patients with angina pectoris. No relationship could be established between this increase in exercise tolerance and that observed in the same 10 patients when 0.3 mg. of nitroglycerin was administered before exercise. An increased exercise tolerance was seen after carotid sinus pressure in patients in whom nitroglycerin was without effect and vice versa. Carotid sinus pressure before exercise did not prevent, as does nitroglycerin, the R-ST segment changes consequent to exertion. The speed of relief of cardiac pain by carotid sinus pressure is also against the hypothesis that coronary vasodilation occurs with consequent improvement in the discrepancy between blood supply and myocardial demand. Continuous electrocardiographic studies were carried out before, during and after carotid sinus pressure in 13 patients during attacks of angina pectoris. No consistent relationship existed between the change in cardiac rate following carotid sinus pressure and the relief of cardiac pain. Marked cardiac slowing was obtained without relief of pain and relief of anginal pain occurred when cardiac slowing was absent or not significant.

3. The doubtful usefulness of carotid sinus pressure as a diagnostic test and a therapeutic measure in angina pectoris are discussed. The

dangers of carotid sinus pressure have been emphasized.

Sumario Español

El efecto de presión sobre el seno carótido en la duración y el carácter de ataques de angina de pecho inducidos por ejercicio bajo condiciones controladas ha sido estudiado en 13 sujetos. Observaciones son presentadas que son consistentes con la hipótesis de que la estimulación del seno carótido induce dolor cardíaco mediante la interrupción de arcos reflejos simpáticos o nervios sensorios. El uso de presión sobre el seno carótido como una prueba diagnóstica y terapéutica en la angina de pecho se discute.

REFERENCES

[1] Freedberg, A. S., Spiegl, E. D., and Riseman, J. E. F.: Effect of External Heat and Cold on Patients with Angina Pectoris: Evidence for the Existence of a Reflex Factor. Am. Heart J. **27:** 611, 1944.

[2] Wasserman, S.: Die Angina Pectoris, Ihre Pathogenese and Pathophysiologie. Wien. klin. Wchnschr. **41:** 1514, 1928.

[3] —, and Weber, H.: Angina Pectoris und Pressorezeptorren-regulation. Acta med. scandinav. **100:** 589, 1939.

[4] D. Danielopolu: Über den Mechanismus der Beendigung des anfalles von Angina Pectoris. Klin. Wchnschr. **8:** 596, 1929.

[5] Flesch, J.: Prognostische Bedeutung des Karotis-Sinusreflexes (Vagusdruckreflex). Wien klin. Wchnschr. **43:** 1318, 1930.

[6] Mandelstamm, M.: Über Subjektive Beschwenken Bei Vegetativen Herzreflex. Das Sensible Karotisphänomen. Ztschr. f. Kreislaufforsch. **24:** 305, 1932.

[7] —: Reflexes Cardiaque Vegetatif dans L'angine de Poitrine. Leur Valeur Diagnostique and Therapeutique. Arch. mal. coeur **25:** 539, 1932.

[8] Wayne, E. J., and Laplace, L. B.: Observations on Angina of Effort. Clin. Sc. **1:** 103, 1933.

[9] Levine, S. A., and Harvey, W. P.: Temporary Relief of Anginal Pain by Carotid Sinus Stimulation. Tr. A. Am. Physicians **60:** 255, 1947.

[10] Freedberg, A. S. and Riseman, J. E. F.: Observations on the Carotid Sinus Reflex and Angina Pectoris. Proc. New England Heart Ass. Page 36, 1948.

[11] Riseman, J. E. F., and Stern, B.: A Standardized Exercise Tolerance Test for Patients with Angina Pectoris on Exertion. Am. J. M. Sc. **188:** 546, 1934.

[12] — and Brown, M. G.: The Duration of Attacks of Angina Pectoris on Exertion and the Effect of Nitroglycerin and Amyl Nitrite. New England J. Med. **217:** 470, 1937.

[13] Freedberg, A. S., Riseman, J. E. F., and Speigl, E. D.: Objective Evidence of the Efficacy of Medicinal Therapy in Angina Pectoris. Am. Heart J. **22:** 494, 1941.

[13a] Riseman, J. E. F.: The Treatment of Angina Pectoris. A Summary of Ten Years' Objective Study. New England J. Med. **229:** 670, 1943.

[13b] —: The Present Status of Treatment in Angina Pectoris. Connecticut State M. J. **9:** 99, February, 1945.

[14] Gregg, D. E.: Coronary Circulation. Physiol. Rev. **26:** 28, 1946.

[15] Wegria, R.: Pharmacology of the Coronary Circulation. Pharmacol. Rev. **3:** 197, 1951.

[16] Freedberg, A. S., Spiegl, E. D., and Riseman, J. E. F.: Octyl Nitrite in the Treatment of Angina Pectoris. Am. Heart J. **22:** 519, 1941.

[17] Weinstein, A. A., and Hoff, H. E.: Mechanism of Relief of Pain Immediately after Total Thyroidectomy for Angina Pectoris and Congestive Failure. Surg. Gynec. & Obst. **64:** 165, 1937.

[18] White, J. C., and Smithwick, R. H.: The Autonomic Nervous System, Anatomy, Physiology and Surgical Application, ed. 2. New York, McMillan. 1941.

[19] Lindgren, I.: Cutaneous Precordial Anaesthesia in Angina Pectoris and Coronary Occlusion. Cardiologia **11:** 207, 1946–1947.

[20] Travell, J., and Rinzler, S. H.: Relief of Cardiac Pain by Local Block of Somatic Trigger Areas. Proc. Soc. Exper. Biol. & Med. **63:** 480, 1946.

[21] Jonnesco, T.: Angine de Poitrine Guerie par la Secretion du Sympathetique Cervico-thoracique. Bull. Acad. Med. **84:** 93, 1920.

[22] White, J. C., and Bland, E. F.: The Surgical Relief of Angina Pectoris: Methods Employed and End Results on 83 Patients. Medicine **27:** 1, 1948.

[23] Heymans, C., Bouckaert, J. J., and Regniers P.: Le Sinus Carotiden et la Zone Homologue Cardio-aortique. Paris, Gaston Doin et Cie., 1933.

[24] Bronk, D. W., Ferguson, L. K., and Solandt, D. Y.: Inhibition of Cardiac Accelerator Impulses by Carotid Sinus. Proc. Soc. Exper. Biol. & Med. **31:** 579, 1934.

[25] Ferris, E. B., Jr., Capps, R. B., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on the Mechanisms of the Unconscious State and Convulsions. Medicine **14:** 377, 1935.

[26] Sigler, L. H.: Hyperactive Cardio-inhibitory Carotid Sinus Reflex. A Possible Aid in the Diagnosis of Coronary Disease. Arch. Int. Med. **67:** 177, 1941.

[27] —: The Hyperactive Cardio-inhibitory Carotid Sinus Reflex as an Aid in the Diagnosis of Coronary Disease. Its Value Compared with that of the Electrocardiogram. New England J. Med. **226:** 46, 1942.

[28] Mandelstamm, M., and Lifshitz, S.: Die Wirkung der Karotissinusreflex auf den Blutdruck beim Menschen. Wien. Arch. inn. Med. **22:** 397, 1932.

[29] Weiss, S., and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease. Its Role in the Causation of Fainting and Convulsions. Medicine, **12:** 297, 1933.

[30] Parry, C. H.: An Inquiry into the Symptoms and Causes of the Syncope Anginosa, Commonly Called Angina Pectoris. London, Cadell and Davis, 1799. P. 167.

[31] Hering, H. E.: Der Karotisdruckversuch München. Med. Wchnschr. **70:** 1287, 1923.

[32] Prusick, B., and Herles, G.: Kongressbericht Deutschen Gesellshaft für Kreislaufforschungs. March 6–7. Quoted from Ztschr. Kreislaufforsch. **25:** 251, 1933.

[33] Blumgart, H. L., Schlesinger, M. J., and Davis, D.: Studies of the Relation of the Clinical Manifestations of Angina Pectoris, Coronary Thrombosis and Myocardial Infarction to the Pathologic Findings. Am. Heart J. **19:** 1, 1940.

[34] Levine, S. A.: Some Notes Concerning Angina Pectoris. Bull. New England M. Centre. **9:** 97, 1947.

[35] Downs, T. M.: Carotid Sinus as Etiological Factor in Sudden Anesthetic Death. Ann. Surg. **99:** 974, 1934.

[36] Askey, J. M.: Hemiplegia Following Carotid Sinus Stimulation. Am. Heart J. **31:** 131, 1946.

[37] Brannon, E. S.: Hemiplegia Following Carotid Stimulation. Am. Heart J. **36:** 299, 1948.

[38] Marmor, J., and Sapirstein, M. R.: Bilateral Thrombosis of Anterior Cerebral Artery Following Stimulation of Hyperactive Carotid Sinus. J.A.M.A. **117:** 1089, 1941.

[39] Zeman, F. D., and Siegal, S.: Monoplegia Following Carotid Sinus Pressure in the Aged. Am. J. M. Sc. **213:** 603, 1947.

[40] Shookhoff, C.: Ventricular Fibrillation with Cardiac Recovery, Caused by Carotid Sinus Pressure, in Case of Auricular Fibrillation. Am. Heart J. **6:** 758, 1931.

[41] Schwartz, I. L., and Eichna, L. W.: Hypersensitive Carotid Sinus Reflex Associated with Spontaneous, Transient Complex Heart Block. Circulation **1:** 922, 1950.

[42] Linenthal, A. J., and Freedberg, S. A.: Measures Used in the Prevention and Treatment of Cardiac Arrhythmias. New England J. Med. **24:** 570, and 612, 1949.

The Effect of Exercise on Coronary Blood Flow, Myocardial Oxygen Consumption and Cardiac Efficiency in Man

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It has been known that exercise causes an increase in the coronary blood flow in animals. The present work has been carried out to study the effect of exercise on coronary blood flow and myocardial oxygen consumption of the human heart in vivo. The results indicate that the heart responds to the increased load of exercise with a rise in coronary blood flow. Since the arteriovenous coronary oxygen difference shows little change, the increase in oxygen consumption of the heart muscle is primarily the result of an increased coronary blood flow. As the cardiac work rises more than the myocardial oxygen consumption, the left ventricular efficiency increases. The response of the failing heart muscle to acute increases in load produced by exercise does not differ from that of the normal heart or of the isolated heart.

CATHETERIZATION of the coronary sinus in man in conjunction with the nitrous oxide method has made it possible to determine coronary blood flow and myocardial oxygen consumption in man.[1,2] Until now, the method has been used to follow the behavior of human heart muscle of resting individuals only.[3] A study of the coronary circulation and myocardial oxygen consumption during exercise would appear to be of interest, because exercise constitutes a temporary increase in load to which the heart must adjust itself by coronary circulatory and metabolic changes. The alterations in the coronary circulation and myocardial oxygen consumption are of particular importance since it is during increased cardiac activity that deficiencies of the coronary circulation become most apparent. It is the purpose of this paper to present data on changes in coronary blood flow, myocardial oxygen consumption and myocardial efficiency in man occurring during moderate exercise and to discuss their significance.

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Methods

Selection of Patients

Thirteen patients with diseases of various etiologies contributed data which form the basis of this report. All patients were studied for diagnostic purposes and coronary blood flows were obtained only after diagnostic catheterization studies had been completed. The nature of the procedure was explained to the patient and his written consent obtained. Two subjects (E. S., R. B.) were mildly anemic (table 1), and three (O. Hr., A. M., W. M.) had hypertensive cardiovascular disease. One of these (O. Hr.), who also was slightly anemic, was on hexamethonium chloride therapy (table 1). Two subjects (A. A., W. R.) had aortic insufficiency and the others suffered from angina pectoris (O. S.), rheumatic heart disease with mitral stenosis (J. Dl.), senile heart disease with auricular fibrillation (J. Df.), thyrotoxicosis (C. T.) and congestive failure, cause unknown (O. Hk.). All patients except O. Hk. were well compensated.

Procedures

The test was performed in the morning after most of these individuals had eaten a small breakfast. Following a one hour rest, respiratory gases were collected in a Douglas bag over a period ranging

TABLE 1.—*Findings Obtained before and after Exercise on 13 Patients with Various Conditions Affecting the Circulation*

Subject	Diagnosis		Cardiac Output cc./min.	Cardiac Index cc./min./M.²	Coronary Arteriovenous O_2 Difference vol. %	O_2 Content Coronary Sinus vol. %	Coronary Flow cc./100 Gm./min.	Coronary Vascular Resistance mm.Hg/cc./100 Gm/min.	Left Ventricular O_2 Consumption cc./100 Gm./min.	Left Ventricular O_2 Consumption cc./min.	Aerobic Energy Uptake of Left Ventricle Kg. Meters	Mean Arterial Pressure mm. Hg	Work of Left Ventricle Kg. Meters	Mechanical Efficiency of Left Ventricle %
X. W.	Normal	Before	8,100	3,850	11.0	6.4	101	0.92	11.2	22.4	44.8	93	10.1	22.7
		After	10,400	4,950	12.1	5.7	101		12.3	24.5	49.0	—	—	—
E. S.	Mild anemia	Before	5,000	3,380	8.5	3.1	69	1.2	5.8	6.1	12.2	85	5.8	47.0
	Hgb. 9.5 Gm.	After	6,260	4,230	9.2	2.8	89		8.2	8.6	17.2	—	—	—
R. B.	Mild anemia	Before	3,870	1,990	7.4	3.0	162	0.55	12.0	19.5	39.0	90	4.8	12.3
	Hgb. 9.4 Gm.	After	11,550	5,920	8.1	2.9	267		21.8	35.4	70.8	—	—	—
A. M.	H. C. V. D.	Before	5,120	3,160	8.1	4.0	111	1.80	9.0	10.7	23.4	197	13.5	57.0
		After	9,789	6,000	8.5	2.7	278	1.45	23.6	28.2	56.3	191	25.5	45.0
W. M.	H. C. V. D.	Before	7,400	3,900	11.8	5.1	80	1.72	9.4	13.2	26.4	138	13.9	52.8
		After	13,900	7,300	12.2	4.6	124	1.10	15.1	21.2	42.4	138	26.0	61.0
O. Hr.	H. C. V. D.	Before	8,255	4,390	6.5	2.6	126	0.85	8.1	13.1	26.2	102	11.5	44.0
	Mild anemia	After	16,276	8,700	7.0	1.7	137	1.04	9.6	15.5	31.0	139	31.0	100.0
A. A.	Aortic	Before	3,240	1,890	9.6	4.4	89	1.13	8.5	13.7	27.4	101	4.4	16.0
	Insufficiency	After	4,720	2,720	9.3	4.6	142	1.01	13.2	21.2	42.4	140	10.9	26.0
W. R.	Aortic	Before	5,150	2,750	10.3	7.5	80	1.00	8.2	13.6	27.2	80	5.6	20.6
	Insufficiency	After		—	—	—	97	0.83				80		
J. Dl.	Mitral	Before	15,400*	7,120	13.0	1.2	112	0.85	14.6	31.0	60.0	95	19.8	32.6
	Stenosis	After	20,000*	9,260	13.0	1.2	149	0.75	19.4	41.5	82.0	112	30.4	37.0
O. S.	Angina	Before	7,250	4,050	11.2	4.3	83	0.92	9.3	14.8	30.4	76	7.5	24.6
	Pectoris	After	—	—	11.8	4.3	109	0.88	12.9	20.6	42.5	96	—	
J. Df.	Auricular	Before	4,700	2,790	10.2	3.9	67	1.14	6.9	8.2	16.4	76	4.9	29.5
	Fibrillation	After	6,900	4,100	9.7	3.6	89	—	8.7	10.3	20.6	—		
O. Hk.	Congestive	Before	5,100	2,890	13.1	5.2	45	1.71	5.9	8.2	17.1	77	5.3	31.0
	Heart Failure	After	6,200	3,500	14.7	4.0	72	1.16	10.6	14.9	30.9	72	6.1	19.6
C. T.	Thyrotoxicosis	Before	9,428	5,290	12.2	7.1	65	1.55	7.9	12.3	24.5	101	12.9	53.0
		After	12,198	6,840	12.3	6.9	86	1.63	10.5	16.3	32.7	140	23.2	71.0

* Benedict-Roth apparatus used.

from two to three minutes for the determination of oxygen consumption and carbon dioxide production. In one patient (J. Dl.) the oxygen consumption was determined with a Benedict-Roth spirometer. The right ventricle was catheterized via the left median antecubital vein and a sample of blood was obtained for the determination of the cardiac output.[4]

Following this, the patient was placed in the right lateral position and the coronary sinus was catheterized. The presence of the catheter in the coronary sinus was determined by the fluoroscopic position of the catheter, the dark color of the blood withdrawn, the shape and height of the pressure,[1a] and by absence of cardiac irregularities.[1a] Successful intubation of the coronary sinus was possible in about 50 per cent of the patients in whom it was attempted. This low incidence is probably the result of anatomic variations in the structure of the right atrium or the coronary ostium.[5] Although untoward effects have been reported to follow catheterization of the coronary sinus,[6] none developed in our patients. This is due to the fact that intubation was attempted only with the patient in the right lateral position. Thus, the correct position of the catheter could be accurately ascertained and the entrance of the catheter into the right ventricle could be avoided. After the catheter had been correctly introduced the patient was placed on his back and an indwelling arterial needle was introduced into the right brachial artery.

With the catheter placed in the coronary sinus, nitrous oxide was administered by the method previously described.[1a] The patient was allowed to breathe the gas mixture for 12 minutes to permit saturation of the heart muscle with nitrous oxide. Just before the end of the saturation period, samples of both coronary sinus and arterial blood were collected for the determination of the nitrous oxide content at full saturation. The patient was then suddenly disconnected from the respiratory system and permitted to breathe room air. Four one-minute samples were drawn simultaneously from the coronary sinus and brachial artery. All blood samples were drawn in Luer-Lok syringes of 10 cc. capacity which had been oiled and which contained 10 drops of heparin.

After the resting observations had been completed, nitrous oxide was again administered for 10 minutes. At the beginning of the eighth minute of nitrous oxide inhalation, exercise was started. It was continued during the collection of the blood samples, until collection of expired air and sampling of right atrial blood had been completed. The total duration of exercise was slightly less than 10 minutes. Exercise was performed in the supine position. It was not mechanically controlled in some subjects (C. W., E. S., O. Hk., O. S., J. Dl., J. Df., A. A., and R. B.), consisting of alternate bicycling motion of the legs against a resistance imposed by the hands of one of us. In the other subjects (O. Hr., W. R., C. T., A. M., W. M.) exercise was performed on a bicycling apparatus by causing the patients to push their feet against two weighted pedals. Using this apparatus, the work performed amounted to approximately 19 kilogram meters per minute.*

Blood pressures were measured with a sphygmomanometer or the strain gauge. In the latter case the pressures were optically recorded. Mean pressures were obtained by adding one-third of the pulse pressure to the diastolic pressure, or by planimetric integration of the area under the pressure curve.

Calculations

Cardiac output was calculated according to the Fick equation:

$$\textit{Cardiac output (in cc./min.)} = \frac{\textit{oxygen consumption (in cc.)}}{\textit{oxygen content arterial blood (vol. \%) minus oxygen content mixed venous blood (vol. \%)}} \times 100$$

The coronary blood flow was calculated according to the method previously described.[1a, b] Gregg has shown that the coronary sinus drains primarily left ventricular muscle. Consequently, the nitrous oxide method measures primarily the flow through a unit (100 Gm.) of left ventricular tissue.[7] Furthermore, Visscher has stated that the oxygen content of the coronary sinus blood does not necessarily represent that of other venous channels draining the myocardium.[8] Therefore, the nitrous oxide method measures blood flow through that unit of muscle only which drains into the coronary sinus. Gregg and his co-workers have found an average variation between the coronary flow per minute per 100 Gm. as determined with the nitrous oxide method and with the rotameter of ± 12.4 per cent.[9]

Coronary vascular resistance was calculated according to the equation:

$$\textit{Coronary vascular resistance (mm. Hg/cc./100 Gm./min.)} = \frac{\textit{mean aortic pressure (mm. Hg)}}{\textit{coronary blood flow (cc./100 Gm./min.)}}$$

The resistance calculated in this manner refers to a unit (100 Gm.) of the coronary vascular bed which drains into the coronary sinus.

The oxygen consumption per 100 Gm. of left ventricular muscle was obtained with the equation:

Oxygen consumption (cc.)/100 Gm. of left ventricular muscle/min. = arterial oxygen content (vol. %) —coronary sinus oxygen content (vol. %) × left ventricular coronary flow (cc./100 Gm. left ventricular muscle/min.)

* Furnished by Respiration Aids Company, New York.

Oxygen consumption of the total left ventricle was obtained with the formula:

Oxygen consumption of left ventricle (cc. oxygen/min.)

$$= \frac{\textit{left ventricular weight}}{100} \times$$

oxygen consumption/100 Gms.

Normal heart weight was calculated from tables of Smith[10] and the left ventricular weight was assumed to be 53 per cent of the total heart weight.[1a]

Since each cubic centimeter of oxygen corresponds to about 2 kilogram meters of energy,[11] the aerobic energy uptake of the left ventricle was calculated as follows:

Aerobic energy uptake of left ventricle (Kg. meters) = oxygen usage in cc./min. × 2.

The work of the left ventricle was obtained from the formula of Starling[12]:

Work (Gm. cm./min.) = cardiac output (cc./min.) × mean aortic pressure (cm. Hg) × 13.6 (specific gravity of mercury).

Gram centimeters per minute were converted to kilogram meters through division by 100,000. Only pressure energy was calculated because the velocity energy of the left ventricle is relatively small.

The relationship of aerobic energy uptake to work of the left ventricle (the mechanical efficiency of the left ventricle) was calculated from the formula:

Mechanical efficiency (per cent)

$$= \frac{\textit{work of left ventricle (Kg. meters/min.)}}{\textit{aerobic energy uptake of left ventricle (Kg. meters/min.)}}$$

Because the weights of hypertrophied hearts could not be accurately observed, left ventricular efficiency could not be calculated in the presence of cardiac hypertrophy. However, by using normal heart weights in patients with hypertrophied left ventricles, maximal values for efficiency were obtained; therefore, if the maximal efficiency was low, true values were even lower. This was shown to be the case in myocardial failure.[3] In assessing the effect of exercise on the heart, individual percentages of efficiency are immaterial but the changes in per cent following exercise are valid.

Analysis

The manometric method of Van Slyke and Neill was used for the determination of oxygen and carbon dioxide in blood.[13] Nitrous oxide was determined according to the method of Kety and Schmidt.[14] The oxygen and carbon dioxide in expired air was analyzed according to the method of Scholander.[15]

Results

Exercise produced a rise in cardiac output of 4066 cc. per minute, which represents a rise of 60 per cent above resting levels (table 1). Similar results were obtained by Hickam and his associates.[16] In one patient (J. Dl.) the cardiac outputs were calculated from oxygen consumptions obtained with a closed circuit method (Benedict-Roth apparatus). It is possible that this accounts for the extremely high value obtained in this individual (table 1).

Previous studies on normal resting subjects have shown that the oxygen content of coronary sinus blood varies from 3.9 to 6.9 volumes per 100 cc.[1a, 2, 3] In this study, only two subjects (C. T., W. R.) exhibited resting values higher than 6.9 volumes per 100 cc. (table 1). All three patients with anemia (E. S., R. B., O. Hr.) and one patient with mitral stenosis (J. Dl.) demonstrated lower than normal values for oxygen content of coronary venous blood at rest (table 1). The oxygen content of coronary sinus blood was determined in 12 of the 13 subjects after exercise (table 1). Nine of this group exhibited a decline in oxygen content ranging from 0.1 to 1.3 volumes per 100 cc.; two showed no change (O. S., J. Dl.), and one (A. A.), revealed a slight rise (table 1).

The left ventricular oxygen extraction (coronary arteriovenous oxygen difference) increased in 10 of the 12 subjects with exercise (table 1). The increase ranged from 0.1 to 1.6 volumes per 100 cc. with an average increase of 0.6 volumes per 100 cc. The largest extraction on exercise occurred in the patient with congestive heart failure (O. Hk., table 1). One subject (J. Dl.) showed no change with exercise, and two (J. Df., A. A.) showed a slight decrease. The resting coronary oxygen extraction was below normal (12 volumes per 100 cc.) in the group with mild anemia (E. S., R. B., O. Hr., table 1). It was normal in the patient with thyrotoxicosis (C. T.), slightly elevated in the subject with mitral stenosis (J. Dl.) and highest in the patient with congestive heart failure (O. Hk.). (See table 1.) Similar findings have been described in a previous publication.[1a]

In all subjects except one (X. W.), exercise produced an increase in the blood flow through

100 Gm. of left ventricular muscle of from 11 to 167 cc. per 100 Gm. per minute, with a mean increase of 43 cc. (table 1). This figure represents an average rise of 45 per cent. Large increements in coronary blood flow were also found by Essex in exercising dogs.[20] It is of interest that increments in coronary blood flow were particularly great in those subjects who exhibited a large rise in cardiac output during exercise (R. B., A. M., W. M., A. A.). In one patient (O. Hr.) the cardiac output increased 97 per cent but the coronary blood flow rose only 8 per cent. This patient was receiving hexamethonium chloride as hypertensive therapy.

The coronary vascular resistance per 100 Gm. declined in seven out of nine patients with exercise (table 1). It is of interest that the coronary vascular resistance also fell in two patients suffering from hypertension (A. M., and W. M., table 1). This indicates that the coronary vascular resistance in this disease may not be fixed. A rise in mean arterial pressure with exercise was noted in a patient with thyrotoxicosis (C. T.) and in one patient with hypertension (O. Hr.). This rise was out of proportion to the increase in coronary blood flow and consequently, coronary vascular resistance increased (table 1). However, one of the patients (O. Hr.) was receiving hexamethonium chloride, which may have prevented further coronary vasodilatation through ganglionic blocking.[17]

Exercise induced a rise in left ventricular oxygen consumption in all patients studied. The increase ranged from 1.1 to 14.6 cc. per 100 Gm. per minute, with an average of 4.9 cc. per 100 Gm. per minute or 65 per cent (table 1). In one patient with anemia (R. B.), one with hypertensive heart disease (A. M.), and in the patient with congestive heart failure (O. Hk.), the increase in myocardial oxygen consumption was especially marked (table 1). It is in these subjects that increments in coronary blood flow with exertion were large. The increase in oxygen consumption per unit of heart weight is of interest because it indicates that an increase in load which occurs with exercise is commensurate with an increase in oxygen usage by the heart.

The increase in left ventricular aerobic energy uptake averaged 48 per cent. The rise was particularly significant in two subjects with hypertension (A. M., W. M.), in one patient with anemia (R. B.), and in the individual with congestive heart failure (O. Hk.). (See table 1.)

Mean arterial pressure was determined in 9 of the 13 subjects before and after exercise. The average elevation in the systemic pressure of five patients was 30 mm. Hg, no change was observed in two, two showed a slight fall with exercise (table 1). These findings are in agreement with those of Ellis[18] and Bock and coworkers.[19]

As the cardiac output rose in all patients, the work of the left ventricle increased. In patients in whom all data were available, the rise in left ventricular work averaged 106 per cent. One patient with hypertension and anemia (O. Hr.) and one with aortic insufficiency (A. A.) showed a very large increase in work (table 1).

In five of seven patients the mechanical efficiency of the left ventricle rose with exercise (table 1). The average increase was 25 per cent. Two patients, one with hypertension (A. M.) and one with congestive failure (O. Hr.) demonstrated a decrease in left ventricular efficiency (table 1). The fall in efficiency noted in the patient with myocardial failure is of particular interest because it indicates that in myocardial failure, as in normal individuals, the oxygen consumption of the left ventricle increases as the load rises. The work of the heart, however, fails to increase proportionately. This results in a disproportionate rise in aerobic energy uptake and therefore in a fall in left ventricular efficiency. The greatest increase in efficiency was noted in the subject with hypertension and anemia who was under treatment with hexamethonium chloride (O. Hr.), and the patient with aortic insufficiency (A. A.). Exercise in these individuals produced large increments in cardiac work with only slight increases in energy uptake.

Discussion

The studies reported in this communication show that moderate exercise increases coronary blood flow without significant change in oxygen

extraction (table 1). This indicates that increases in load are met primarily by a rise in coronary blood flow. This result can be anticipated from previous studies on the hearts of normal resting subjects.[2, 3] It has been stated that the average coronary blood flow in normal resting subjects is 77 cc. per 100 Gm. per minute, the average oxygen consumption is 9.4 cc. per 100 Gm. per minute, and the average oxygen extraction is 12 volumes per 100 cc.[2] Therefore, the total coronary blood flow for a heart weighing 300 Gm. is approximately 240 cc. or 5 per cent of the cardiac output. This is a small figure when compared with the larger volume of blood which perfuses the kidney[21] or the liver.[22] This indicates that the hearts of resting subjects are already extracting a very large amount of oxygen and increases in metabolic demands must be met primarily by a rise in coronary blood flow.

It is of some interest that in a patient (O. S.) who had previous anginal attacks with exertion, pain did not develop during the test. As the oxygen extraction did not change in this subject, the increase in coronary blood flow must have been sufficient for the increased metabolic demands of the heart muscle during exercise.

Associated with increases in coronary blood flow due to exercise, a decline in coronary vascular resistance was noted in seven of nine individuals in whom blood pressures were recorded during exercise (table 1). In two of the seven, hypertension was present. It has been previously stated that in essential hypertension the coronary vascular resistance is increased.[2] A decline in coronary vascular resistance during exercise observed in these individuals illustrates that the increase in resistance is functional rather than anatomic. This is in accordance with work previously published by Smith,[21] Scheinberg,[24] Prinzmetal,[25] Pickering[26] and Wilkins,[27] who found that the vascular resistances of the renal, cerebral, muscular and hepatic beds are not fixed.

The increase in oxygen consumption per unit of left ventricular muscle noted with exercise averaged 65 per cent. The rise in cardiac oxygen consumption is in line with the findings of Starling and Visscher[28] and Evans[29] on the heart-lung preparation. These investigators found that an increase in diastolic volume of the heart in vitro is accompanied, within limits, by an increase in the oxygen usage of the heart. It has been stated previously that a chronic increase in diastolic volume, such as is seen in patients with congestive heart failure, does not lead to a rise in oxygen uptake of the heart per unit weight. In line with this observation is the finding that the oxygen usage per 100 Gm. of left ventricular muscle in patient O. Hk., who suffered from congestive heart failure, is not elevated (5.9 cc. oxygen per 100 Gm., as compared with a normal of 7.8 cc., table 1). It is of particular significance that in this patient exercise did result in increased oxygen uptake of the myocardium (from 5.9 to 10.6 cc. per 100 Gm. of left ventricular muscle, table 1). This demonstrates that the response of the failing heart muscle to acute increases in load does not differ from that of the normal human heart in vivo or the isolated heart in vitro. These findings again show the difference in response of the heart to acute and chronic changes in diastolic volume.

The mechanical efficiency of the left ventricle increased in five of seven patients in whom all data for the calculations are available (table 1). Although the aerobic energy uptake of the left ventricle rises with exercise, the work of the left ventricle rises to a greater degree. This denotes that an increase in load of the normal heart leads to a more effective conversion of oxidative energy into useful work. This is in agreement with findings obtained in this laboratory which showed that as the work of the heart increases, the ratio of mechanical work to energy derived from the aerobic breakdown of glucose rises also.[30] It is possible therefore that the cause of a more effective conversion of aerobic energy by the heart working with an increased load may be a more efficient utilization of glucose.

The left ventricular efficiency of the patient with myocardial failure declined during exercise. This is the result of both the considerable rise in myocardial oxygen consumption (80 per cent) and of a relatively small increase in cardiac output (22 per cent). Apparently the myocardium had reached the state where any fur-

ther acute increase in load failed to elicit a proportional augmentation of stroke volume; evidence of the existence of myocardial depression or failure.

A decline in mechanical efficiency during failure has been previously noted.[1a] The observation that exercise leads to a further fall in mechanical efficiency denotes that the conversion of aerobic energy into useful work in failure becomes increasingly more impaired as the load progresses. In line with this is the finding that in myocardial failure the energy equivalent of the glucose extracted by the heart muscle is considerably greater than the work performed.[30] Thus, the failing heart appears to be unable to make full use of its aerobic energy as well as the energy derived from the breakdown of glucose.

Summary

The effect of exercise on the coronary circulation, myocardial oxygen consumption and efficiency was studied in 13 subjects by means of the nitrous oxide method in conjunction with catheterization of the coronary sinus.

The coronary blood flow per 100 Gm. of left ventricular muscle increased after exercise without significant changes in the oxygen extraction. The rise in coronary blood flow per 100 Gm. of left ventricular muscle averaged 45 per cent. An average increase of 63 per cent in cardiac output during exercise was observed.

The oxygen consumption per 100 Gm. of left ventricular muscle rose an average of 65 per cent. The rise in myocardial oxygen consumption with exercise noted in a patient with congestive heart failure demonstrated that the response of the failing heart muscle to acute increases in load does not differ from that of the normal human heart or the isolated heart.

The increase in left ventricular work observed during exercise was proportionately greater than the rise in left ventricular oxygen consumption. Consequently, the left ventricular efficiency increased. In the patient with myocardial failure, the left ventricular efficiency declined.

A fall in coronary vascular resistance was observed in most of the patients including those with hypertension. This indicated that the increase in coronary vascular resistance in hypertension is functional.

The significance of these findings is discussed.

Sumario Español

Se sabe que en los animales el ejercicio produce un incremento en la circulación coronaria. El trabajo presente se condujo para estudiar el efecto del ejercicio en la circulación coronaria y la consunción de oxígeno del miocardio en el corazón humano vivo. Los resultados indican que el corazón responde al incremento en carga de ejercicio con un aumento en circulación coronaria. Como la diferencia de oxigenación arteriovenosa muestra muy poco cambio, el aumento en consunción de oxígeno del miocardio es primeramente el resultado de un aumento en circulación coronaria. A medida que el trabajo del corazón aumenta más que la consunción de oxígeno por el miocardio, la eficiencia del ventrículo izquierdo también aumenta. La manera en que un corazón que está decompensándose responde a incrementos agudos en trabajo producidos por ejercicio no difiere en nada del corazón normal o del corazón aislado.

REFERENCES

[1a] Bing, R. J., Hammond, M. M., Handelsman, J. C., Powers, S. R., Spencer, F. C., Eckenhoff, J. E., Goodale, W. T., Hafkenschiel, J. H., and Kety, S. S.: The measurement of coronary blood flow, oxygen consumption, and efficiency of the left ventricle in man. Am. Heart J. **38:** 1, 1949.

[1b] Eckenhoff, J. E., Hafkenschiel, J. H., Harmel, M. M., Goodale, W. T., Lubin, M., Bing, R. J., and Kety, S. S.: Measurement of coronary blood flow by the nitrous oxide method. Am. J. Physiol **152:** 356, 1948.

[2] Bing, R. J.: The coronary circulation in health and disease as studied by coronary sinus catheterization. Bull. New York Acad. Med. **27:** 407, 1951.

[3] —, Daley, R.: Behavior of the myocardium in health and disease as studied by coronary sinus catheterization. Am. J. Med. **10:** 711, 1951.

[4] Cournand, A., and Ranges, H. A.: Catheterization of right auricle in man. Proc. Soc. Exper. Biol. & Med. **46:** 462, 1941.

[5] Hellerstein, H. K., and Orbison, J. L.: Anatomic variations of the orifice of the human coronary sinus. Circulation **3:** 514, 1951.

[6] McMichael, J., and Mounsey, J. P. D.: A complication following coronary sinus and cardiac vein catheterization in man. Brit. Heart J. **13:** 397, 1951.

[7] Gregg, D. E.: Coronary Circulation in Health and Disease. Philadelphia, Lea and Febiger, 1950.

[8] Visscher, M. B.: Blood, heart and circulation. Publication of the American Association for the Advancement of Science. No. 13, 1940.

[9] Gregg, D. E., Longino, F. H., Green, P. A., and Czerwonka, L. J.: Comparison of coronary flow determined by the nitrous oxide method and by a direct method using the rotameter. Circulation **3:** 89, 1951.

[10] Smith, H. L.: The relation of the weight of the heart to the weight of the body and the weight of the heart to age. Am. Heart J. **41:** 79, 1928.

[11] Landowne, M., and Katz, L. N.: Circulatory system: heart; work and failure. In: Medical Physics. Chicago, Year Book Publishers, 1950. Vol. 2, pp. 194–206.

[12] Starling, E. H., and Evans, C. L.: Respiratory exchanges of the heart in the diabetic animal. J. Physiol. **49:** 67, 1914–1915.

[13] Van Slyke, D. D., and Neill, J. M.: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. J. Biol. Chem. **61:** 523, 1924.

[14] Kety, S. S., and Schmidt, C. F.: The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations. Am. J. Physiol. **143:** 53, 1945.

[15] Scholander, P. F.: Analyzer for accurate estimation of respiratory gases in one half cubic centimeter samples. J. Biol. Chem. **167:** 235, 1947.

[16] Hickam, J. B., and Cargill, W. H.: Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. J. Clin. Investigation **27:** 10, 1948.

[17] Moe, G. K., and Freyburger, W. A.: Ganglionic blocking agents. Pharmacol. Rev. **2:** 61, 1950.

[18] Ellis, L.: Circulatory adjustments to moderate exercise in normal individuals, with particular reference to the interrelation between the velocity and volume of the blood flow. Am. J. Physiol. **101:** 494, 1932.

[19] Bock, A. V., Vancaulaert, C., Dill, D. B., Folling, A., and Hurxthal, L. M.: Studies in muscular activity III. J. Physiol. **66:** 136, 1928.

[20] Essex, H. E., Herrick, J. F., Baldes, E. J., and Mann, F. C.: Influence of exercise on blood pressure, pulse rate, and coronary blood flow of the dog. Am. J. Physiol. **125:** 614, 1939.

[21] Smith, H. W.: The Kidney; Structure and Function in Health and Disease. New York, Oxford University Press, 1951.

[22] Bradley, S. E., Ingelfinger, F. J., Bradley, G. P., and Curry, J. J.: Estimation of hepatic blood flow in man. J. Clin. Investigation **24:** 890, 1945.

[23] Katz, L. N., Wise, W., and Jochim, K.: Control of the coronary flow in the denervated isolated heart and heart-lung preparation of the dog. Am. J. Physiol. **143:** 479, 1945.

[24] Scheinberg, P., Jayne, H. W.: Factors influencing cerebral blood flow and metabolism. Circulation **5:** 225, 1952.

[25] Prinzmetal, M., Wilson, C.: The nature of peripheral resistance in arterial hypertension with special reference to the vasomotor system. J. Clin. Investigation **15:** 63, 1936.

[26] Pickering, G. W.: Peripheral resistance in persistent arterial hypertension. Clin. Sc. **2:** 209, 1936.

[27] Wilkins, R. W., Freis, E. D., Stanton, J. R.: Essential hypertension. Laboratory studies in human beings with drugs recently introduced. J. A. M. A. **140:** 261, 1949.

[28] Starling, E. H., Visscher, M. B.: The regulation of the energy output of the heart. J. Physiol. **62:** 243, 1926.

[29] Evans, C. C.: Recent advances in physiology, ed. 5. Philadelphia, Blakiston, 1936.

[30] Taeschler, M., and Bing, R. J.: Unpublished observation.

Normal and Impaired Retinal Vascular Reactivity

By H. O. Sieker, M.D., and J. B. Hickam, M.D.

Normal retinal arteries and veins will constrict when the arterial blood oxygen tension is increased and dilate when it is lowered. A technic, employing fundus photography, is described for measuring this reaction. The amount of constriction on breathing oxygen, and its trend with age, have been measured in normal subjects. The arteries of persons with well-established hypertension and diabetes usually show marked impairment of this constrictor reaction, presumably because of sclerotic changes. It is suggested that measurements of this reaction may prove to be a useful, quantitative extension of present retinal vascular grading technics.

DURING life, vascular disease is evident mostly through the secondary effects of ischemia in various organs. These are late effects and there is need for the development of more direct and sensitive means of finding and quantitating degenerative vascular disease. Clinically, ophthalmoscopic examination has been valuable in estimating the condition of blood vessels, especially the arteries, because the vessels of the retina often show structural abnormalities in persons with generalized vascular disease. Attempts have been made to quantitate pathologic alterations in these vessels by various grading systems which depend upon visible changes.

In 1940, Cusick, Benson, and Boothby[1] found that normal retinal vessels dilate when a subject breathes gas with a low oxygen tension and constrict when he breathes tank oxygen. The finding has been confirmed.[2, 3] This phenomenon must depend, in part at least, upon the presence of a mobile vessel wall. In view of the likelihood that this reaction would be impaired in persons with retinal vascular sclerosis, and the need for more quantitative estimates of vascular damage, the present study was undertaken. The purpose of this study was to establish the normal range of retinal vascular response to change in oxygen tension, and to determine to what extent the reaction may be altered in persons with known vascular disease.

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Methods

Eyeground photographs were made with a Bausch and Lomb fundus camera while the subjects breathed air, tank oxygen, and, in some cases, 10 per cent oxygen and 90 per cent nitrogen; or 5 per cent carbon dioxide, 21 per cent oxygen and 74 per cent nitrogen. The visible diameter of the larger vessels near the disc was measured from the photographs, using a low-power (9×) dissecting microscope having a scale in the ocular. The range of actual vessel diameter was in the order of 90 to 180 microns. The negative of a normal eye represents a magnification of approximately 3 diameters, and the photographs were 4 diameter enlargements.

As a standard procedure "retinal vascular reactivity" was measured as per cent shrinkage in vessel diameter when a subject breathed first air and then tank oxygen. In a normal subject there is considerable variation in the degree of shrinkage from vessel to vessel when the subject breathes oxygen. For this reason, multiple measurements are required. As a rule, measurements were made at identical points of all the larger vessels in each eye which were clearly defined in photographs made while the subject was breathing different gas mixtures. A given vessel usually shrinks uniformly between bifurcations, but the branches may show motility different from the parent vessel. In general, 6 to 12 measurements were made for both arteries and veins, and the results averaged. The reproducibility of the measurement method was studied on duplicate series of photographs. Estimates of over-all caliber change are reproducible within 2 per cent.

Trials on normal subjects indicate that retinal vascular constriction is substantially complete within five minutes after passing from breathing air to

breathing tank oxygen, and this was the standard time used in the study.

A larger change in vascular diameter can be produced in normal subjects by passing from 10 per cent oxygen to tank oxygen, but this method has two disadvantages for general use. The low oxygen mixture could be hazardous for subjects with vascular disease. In addition, the arterial oxygen tension on 10 per cent oxygen is quite variable. Uniformity of stimulus would be hard to achieve and would require oximetric control. Table 1 shows the results obtained with 10 per cent oxygen and 99.6 per cent oxygen in a small series of normal young subjects. On 10 per cent oxygen the per cent oxygen saturation of brachial arterial blood ranged from 59 to 84 per cent in this group.

TABLE 1.—*Comparative Effect of High and Low Oxygen Tensions on Retinal Vessels in 11 Normal Eyes*

% O_2 Breathed	Arterial Reactivity*	Venous Reactivity*
99.6	13.6 ± 1.6†	15.0 ± 2.1
10	10.1 ± 1.1	10.0 ± 1.0

* Expressed as per cent change from vessel diameter while breathing air.

† Standard error.

Parallel trials of the effects of breathing a mixture of 5 per cent carbon dioxide, 21 per cent oxygen, and 74 per cent nitrogen, and of 99.6 per cent oxygen have been made in 20 normal subjects and patients with vascular disease. By the present method of measurement, 5 per cent carbon dioxide has very little effect on the larger retinal vessels, although it is known to cause a considerable increase in cerebral blood flow.

RESULTS

1. *Normal Retinal Vascular Reactivity*

Measurements of retinal vascular reactivity, as average per cent decrease in vessel diameter on passing from air to tank oxygen, were made in 31 normal subjects. There were 26 males and five females. The mean age was 37.4 years (standard deviation 17.8), with the extremes being 17 and 83 years. The subjects were medical students and hospital patients. None showed evidence of vascular disease by history and physical examination.

The mean arterial reactivity was 11.5 per cent (standard error 0.8), and the mean venous reactivity was 14.0 per cent (S.E. 1.0). The regression of arterial reactivity on age is presented in figure 1. There is a significant negative correlation between arterial reactivity and age ($r = -.381, t = 2.215, .02 < p < .05$). The tendency is to lose reactivity at about the rate of 1 per cent every 10 years. In this group, no subject below the age of 55 had an arterial reactivity under 6.0 per cent. The correlation between age and venous reactivity is not at a significant level. There is, however, a significant positive correlation between arterial reactivity and venous reactivity for the group as a whole ($r = .565, t = 3.68, p < .01$). That is, there is a tendency for a high order of arterial reactivity to be associated with a high order of venous reactivity, and vice versa.

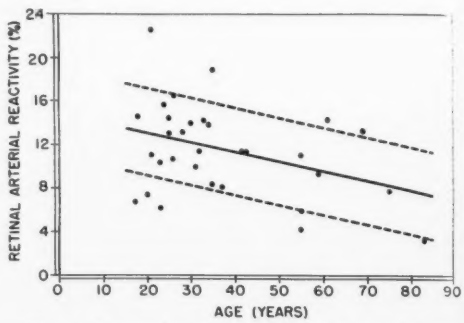


FIG. 1. Regression of retinal arterial reactivity on age in 31 normal subjects. The regression line is $Y = 14.9 - .09X$, where Y is reactivity (measured as per cent decrease in vessel diameter on breathing oxygen), and X is age in years. The standard deviation from regression is 4.0. Below age 55, arterial reactivity did not fall under 6 per cent.

An example of normal reactivity is shown in figure 2.

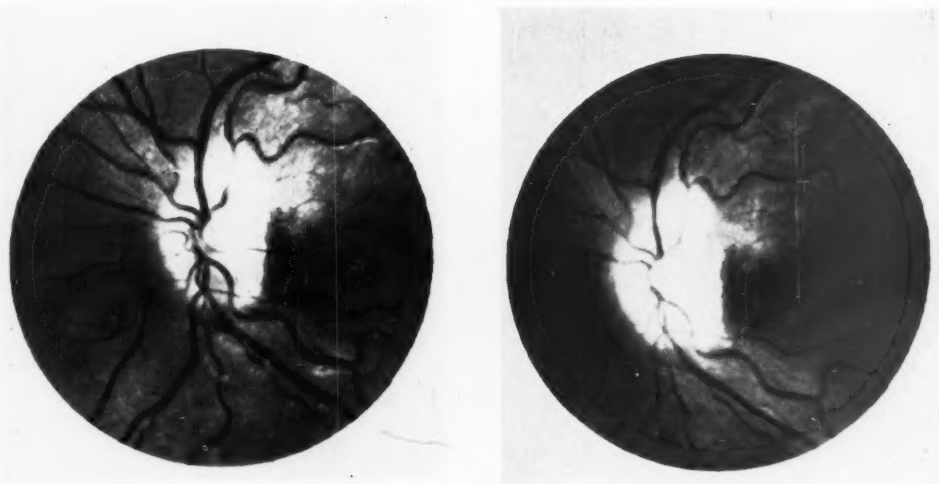
2. *Retinal Vascular Reactivity in Hypertension*

Measurements of reactivity were made in 29 hypertensive subjects. The criteria for hypertension were a systolic pressure usually over 150 or a diastolic pressure usually over 90 mm. Hg. These limits were ordinarily considerably exceeded. There were 23 males and six females. The mean age was 49.7 years (S.D. 10.0). The mean arterial reactivity was 3.2 per cent (S.E. 0.8). This is significantly different from normal ($t = 7.390, p < .01$). The three best reactivities in the group were

7.0 per cent (male, age 48, blood pressure 162/95), 15.8 per cent (male, age 45, blood pressure 218/128) and 20.2 per cent (male, age 35, blood pressure 174/120). Venous reactivity was much less impaired. The mean venous reactivity was 10.9 per cent (S.E. 0.9). This is still significantly different from normal ($t = 2.318$, $.02 < p < .05$).

As a group, these patients were severe hypertensives. Several of them had had cerebral vascular accidents or myocardial infarctions.

40.4 years (S.D. 15.4). The mean arterial reactivity was 3.0 per cent (S.E. 0.9). This is significantly different from normal ($t = 6.750$, $p < .01$). Many members of this group had severe diabetes, with complications such as retinopathy, neuropathy, hypertension, and coronary or peripheral arterial insufficiency. Three subjects, who were nonhypertensive, had arterial reactivities within the normal range. The venous reactivity of the group was 9.2 per cent (S.E. 1.4). This is also significantly different from normal ($t = 2.824$, $p < .01$).



Air O_2

FIG. 2. Constriction of normal retinal vessels resulting from inhalation of 99.6 per cent oxygen. The subject is a 21 year old male

Through the courtesy of Dr. Walter Kempner, four patients were studied before and after four months on the rice diet.[4] These patients had a substantial reduction in blood pressure but no pronounced change in arterial reactivity. The data are presented in table 2. This result is pertinent because it demonstrates that loss of arterial reactivity in hypertension is not caused simply by a high internal distending pressure which mechanically resists constriction.

TABLE 2.—*Retinal Vascular Reactivity in Hypertensives on the Rice Diet*

Patient	Age	State	B.P.	Arterial Reactivity	Venous Reactivity
M.S.	51	Before diet	190/122	2.7	12.9
		On diet 4 mo.	135/90	1.2	11.3
M.R.	41	Before	183/128	0.5	10.6
		On diet 4 mo.	109/81	5.1	15.0
R.H.	64	Before	160/100	2.6	17.4
		On diet 4 mo.	110/68	3.8	13.1
B.C.	53	Before	180/110	3.4	11.6
		On diet 4 mo.	142/77	4.0	16.4

Retinal Vascular Reactivity in Diabetes

Reactivity was measured in 16 subjects, 11 males and five females. The mean age was

In order to distinguish the effect of diabetes, per se, from that of hypertension, reactivities were calculated separately for those diabetics who had never had hypertension, so far as could be determined. There were 10 of these, having a mean age of 41.4 years (S.E. 16.0). The arterial reactivity was 4.2 per cent (S.E. 1.4), significantly different from normal ($t = 4.710$, $p < .01$). The venous reactivity was 10.6 per cent (S.E. 1.6), which is not significantly different from normal.

The results obtained on normal, hypertensive and diabetic subjects are summarized in table 3.

TABLE 3.—*Retinal Vascular Reactivity to 99.6 Per Cent Oxygen*

Subjects	Number	Age	Arterial Reactivity	Venous Reactivity
Normal	31	37.4	11.5±0.8	14.0±1.0
Hypertensive	29	49.7	3.2±0.8*	10.9±0.9*
Diabetic	16	40.4	3.0±0.9*	9.2±1.4*
Nonhypertensive diabetic	10	41.4	4.2±1.4*	10.6±1.6

* Significantly different from normal.

DISCUSSION

The means of expressing retinal vascular reactivity deserves some comment. The functional result of vessel motility is to regulate flow, and it would be desirable to express retinal vascular reactivity directly in terms of resultant flow changes. However, it is only changes in internal diameter of the larger retinal vessels which can be measured at present, and it would be hazardous to attempt to translate diameter changes in the measurable arteries into terms of vascular resistance and thence into flow. In defense of the present method, it can be said that per cent decrease in diameter is directly related to per cent decrease in circumference, and the measurement, for arteries at least, is a direct expression of constrictor activity of the vessel wall at the point where the measurement is made.

The observations on the effect of altered oxygen tension in normal man are in agreement with those of Cusick, Benson and Boothby[1] and of later investigators,[2, 3] but the changes, by the present technic, are somewhat smaller than those originally described.[1] We do not confirm the finding of Huerkamp and Rittinghaus[3] that carbon dioxide causes a dilatation of the retinal vessels.

There is strong presumptive evidence that the loss of arterial reactivity which occurs in hypertensives and diabetics results from sclerosis of the retinal arteries. Retinal arteriosclerosis, as well as generalized arteriosclerosis, is extremely common in these disorders. It is more difficult to ascribe loss of venous reactivity simply to vessel wall changes, although retinal venous sclerosis is common in hypertensives and diabetics.[5] It is possible that venous caliber changes may be dependent in part upon changing pressure and flow, and that failure of veins to change size is simply a reflection of failure to change flow rate through the arterial system.

As would be expected, there is a rough relationship between clinical grading of arteriosclerotic changes by ophthalmoscopic examination and the impairment of retinal arterial reactivity. Marked "sclerotic" changes are nearly always associated with marked loss of reactivity. However, there have been several instances of marked reduction in arterial reactivity in which the vessels appeared only slightly altered on examination by an experienced internist.

It is probable that measurement of arterial reactivity would be a useful extension of present retinal arterial grading technics from the viewpoints of both sensitivity and quantitation.

SUMMARY

1. "Retinal vascular reactivity" is defined as the average per cent decrease of diameter of visible vessel which occurs when a subject passes from breathing air to breathing tank oxygen. A technic is described for measuring this change by fundus photography.

2. Measurements of retinal vascular reactivity have been made in 31 normal people. There is a slight but statistically significant decline in arterial reactivity with age.

3. Retinal vascular reactivity was measured in 29 hypertensive and 16 diabetic patients.

In both of these groups arterial reactivity was greatly diminished below normal. A few subjects in each group showed reactivity within the normal range.

4. It is believed that the decrease in arterial reactivity of hypertensive and diabetic persons is the result of sclerotic changes in the retinal arteries.

5. Measurement of retinal vascular reactivity may prove to be a useful extension of present retinal vascular grading technics.

Sumario Español

Las arterias y venas retinales se contraen cuando la tensión de oxígeno arterial es aumentada y se dilatan cuando disminuye. Una técnica para medir el cambio mediante fotografía del fondo se describe. La cantidad de contracción al inhalar oxígeno y el cambio que ocurre con edad se ha determinado en sujetos normales. Las arterias de personas con hipertensíon estabelcida y diabetis usualmente muestran deterioro de esta reacción de contracción, presumiblemente dibido a cambios escleróticos. Se sugiere que determinaciones de esta reacción pueden probar provechosas como una extensión quantitativa de las técnicas presentes para la gradación vascular retinal.

REFERENCES

[1] Cusick, P. L., Benson, O. O., Jr., and Boothby, W. M.: Effect of anoxia and of high concentrations of oxygen on the retinal vessels: Preliminary report. Proc. Staff Meet. Mayo Clin. **15:** 500, 1940.

[2] Duguet, J., Dumont, P., and Bailliart, J.: The effects of anoxia on retinal vessels and retinal arterial pressure. J. Aviation Med. **18:** 516, 1947.

[3] Huerkamp, B., and Rittinghaus, F. W.: Über die Blutversorgung der menschlichen Retina unter die Einwirkung veränderter Sauerstoffspanning, von Kohlensäure, Hyperventilation und Adrenalin. Pflügers Arch. ges. Physiol. **252:** 312, 1950.

[4] Kempner, W.: Treatment of heart and kidney disease and of hypertensive and arteriosclerotic vascular disease with the rice diet. Ann. Int. Med. **31:** 821, 1949.

[5] Agatston, S. A.: Clinicopathologic study of diabetic retinitis. Arch. Ophth. **24:** 252, 1940.

The Relation between Retinal and Cerebral Vascular Reactivity in Normal and Arteriosclerotic Subjects

By J. B. Hickam, M.D., J. F. Schieve, M.D., and W. P. Wilson, M.D.

It has been found that retinal arterial reactivity to oxygen is diminished in persons with retinal arteriosclerosis, and that cerebral blood flow and the increment in cerebral flow upon inhalation of carbon dioxide are diminished in persons with cerebral arteriosclerosis. The present study demonstrates that there is a significant positive correlation between retinal arterial reactivity on the one hand, and cerebral blood flow and reactivity, on the other. This finding is taken to mean that arteriosclerosis severe enough to affect measurements of this sort is apt to involve retinal and cerebral vessels together.

BECAUSE of their unique accessibility, the retinal vessels are routinely inspected during the course of a physical examination, and, from their condition, inferences are often made as to the condition of vessels of similar size in other body regions. It is an important clinical question whether such inferences have validity. On the basis of histologic examination, Alpers, Forster, and Herbut[1] have concluded that the relation between cerebral and retinal arteriosclerosis is not particularly close. It is now possible to assess the relation between disease of vessels in these two regions by functional tests which measure the reactivity of the vessels in the fundus and brain.

It has been found that persons with retinal arteriosclerosis have impairment of the constrictor response shown by normal retinal arteries when the subject inhales oxygen.[2] It has also been found that persons with cerebral arteriosclerosis not only have a diminished cerebral blood flow,[3, 4] but also have less than the normal increase in cerebral flow in response to inhalation of carbon dioxide.[4] It is the purpose of the present study to determine whether retinal and cerebral vascular disease, as determined by measurements of this kind, coexist with significant frequency. To this end, measurements of retinal vascular reactivity to oxygen, and of cerebral blood flow and cerebral vascular reactivity to carbon dioxide have been made together in a group which includes normal persons, persons with overt cerebral vascular disease, and persons having illnesses commonly associated with generalized arteriosclerosis.

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Methods

Retinal vascular reactivity was determined, as previously described,[1] from measurements made on fundus photographs, and was expressed as the average per cent decrease in visible vessel diameter which resulted when the subject changed from breathing air to breathing tank oxygen. The measurement was made separately for arteries and veins. Cerebral blood flow was measured by the method of Kety and Schmidt[5] as modified by Scheinberg and Stead.[6] The increase in cerebral blood flow ("cerebral vascular reactivity") after five minutes' administration of 5 per cent carbon dioxide or 7 per cent carbon dioxide was estimated from the decrease in cerebral arteriovenous oxygen difference, as described by Schieve and Wilson.[4]

Results

1. *Correlation between Retinal Vascular Reactivity and Cerebral Blood Flow*

Since the cerebral blood flow is known to be diminished in diffuse cerebral vascular disease, a test was made of the correlation between

resting cerebral blood flow and the retinal vascular reactivity to oxygen. This was done in 31 subjects. These subjects included normal persons over a wide age range, persons who had had cerebral vascular accidents, hypertensives, diabetics, patients with senile dementia, and others. The mean cerebral blood flow of the group was 53.1 (S.D. 15.2) cc. per 100 Gm. per minute (mean normal: 59, S.D. 11[4]); the retinal arterial reactivity was 9.5 per cent, standard deviation 5.8 (mean normal 11.5, 4.2); and the venous reactivity was 15.8 per cent, standard deviation 7.2 (mean normal 14.0, S.D. 5.6).

The pertinent results are presented graphically in figure 1, which relates retinal arterial reactivity to cerebral blood flow. There

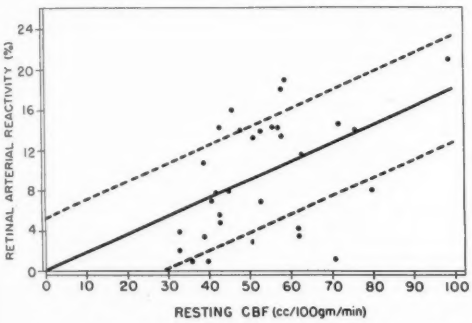

FIG. 1. Correlation between retinal arterial reactivity and resting cerebral blood flow in 31 subjects. Correlation coefficient = .465, $t = 2.820$, $p < .01$. The regression of reactivity on flow is $Y = .18X$. The standard deviation from regression is 5.3.

is a significant positive correlation between the two ($r = .465$, $t = 2.820$, $p < .01$). It will be noted from figure 1 that there are a number of instances in which reactivity and flow are not closely related, some persons having a poor reactivity but good flow, while some show good reactivity but a subnormal flow.

The correlation between retinal venous reactivity and cerebral blood flow is not at a significant level.

2. *Correlation between Retinal Vascular Reactivity to Oxygen and Increase in Cerebral Blood Flow in Response to Carbon Dioxide*

This relationship is of interest because it compares a function of motility in retinal vessels with a function of motility in cerebral vessels. Schieve and Wilson[4] have shown that persons with cerebral vascular disease have significantly less increase in cerebral blood flow on breathing carbon dioxide than do normal persons.

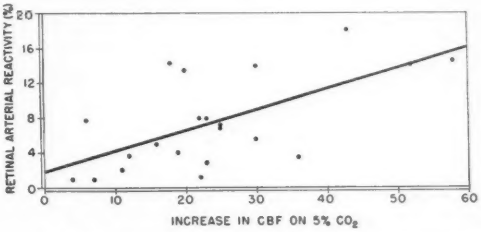

FIG. 2. Correlation between retinal arterial reactivity to oxygen and increase in cerebral blood flow on inhalation of 5 per cent carbon dioxide in 21 subjects. The correlation is highly significant ($r = .632$, $t = 3.550$, $p < .01$). The regression of reactivity on flow change is $Y = .234X + 1.8$. The standard deviation is 4.2.

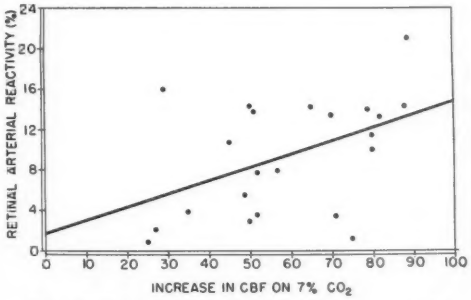

FIG. 3. Correlation between retinal arterial reactivity to oxygen and increase in cerebral blood flow on inhalation of 7 per cent CO_2 in 22 subjects. The correlation is significant ($r = .463$, $t = 2.330$, $.02 < p < .05$), but not so good as for 5 per cent carbon dioxide. The regression of reactivity on flow change is $Y = .13X + 1.7$.

Trials were made with both 5 per cent and 7 per cent carbon dioxide. The effect of both gases was tried in 15 subjects. In all, 21 subjects had 5 per cent carbon dioxide and 22 had 7 per cent carbon dioxide.

For the group on 5 per cent carbon dioxide, the mean increase in cerebral blood flow was 24 cc. per 100 Gm. per minute (mean normal 30 cc.[4]), and the retinal arterial reactivity was

7.4 per cent. For the group on 7 per cent carbon dioxide, the mean increase in flow was 59 cc. (mean normal 70 cc.), and the retinal arterial reactivity was 9.4 per cent.

The data on retinal arterial reactivity and cerebral blood flow increase on 5 per cent carbon dioxide are presented in figure 2. There is a highly significant positive correlation ($r = .632$, $t = 3.550$, $p < .01$). Venous reactivity was also significantly correlated with flow change, but less closely ($r = .489$, $t = 2.430$, $.01 < p < .02$).

The data on arterial reactivity and cerebral flow change in the group receiving 7 per cent carbon dioxide are presented in figure 3. The correlation is again significant ($r = .463$, $t = 2.330$, $.02 < p < .05$), but not so highly significant as in the group receiving 5 per cent carbon dioxide. Venous reactivity was not significantly correlated with flow change.

In the over-all picture, retinal arterial reactivity is significantly correlated with the resting cerebral blood flow and with the increase in flow which results from the inhalation of carbon dioxide. The closest correlation, and one which is statistically highly significant, is that between retinal arterial reactivity and the increase in cerebral flow on 5 per cent carbon dioxide. Retinal venous reactivity, in general, correlates poorly with these functions of the cerebral circulation.

Discussion

Persons with retinal arteriosclerosis have a decreased retinal arterial reactivity.[1] Persons with cerebral arteriosclerosis have a decreased cerebral blood flow and cerebral vascular reactivity.[3, 4] In a group which includes normal and arteriosclerotic persons, retinal arterial reactivity is significantly correlated with cerebral flow and reactivity. It appears from this that arteriosclerosis which is advanced enough to affect these measurements is apt to involve both retinal and cerebral vessels. There are certainly exceptions to this generalization. These are apparent on inspection of the figures.

Inspection of figures 2 and 3 suggests the possibility of making further generalizations as to what the retinal arterial reactivity of a subject may mean in terms of cerebral vascular reactivity. A markedly reduced retinal arterial reactivity suggests, but certainly does not guarantee, a subnormal cerebral vascular reactivity. On the other hand, an average or above average retinal arterial reactivity is quite apt to be associated with a cerebral vascular reactivity within the normal range.

It is concluded that retinal arterial reactivity has extrapolative significance in terms of the cerebral circulation.

Summary and Conclusions

1. Parallel measurements of retinal arterial reactivity to oxygen, on the one hand, and cerebral blood flow and cerebral vascular reactivity to carbon dioxide, on the other, have been made in normal and arteriosclerotic subjects.

2. Retinal arterial reactivity is significantly correlated with cerebral flow and reactivity.

3. This finding is taken to mean that arteriosclerosis severe enough to affect measurements of this sort is apt to involve retinal and cerebral vessels together. There are definite exceptions to this generalization.

Sumario Español

Se ha encontrado que la reactividad arterial retinal al oxígeno esta disminuida en personas con arteriosclerosis retinal y que la circulación cerebral al inhalar bioxido de carbono disminuye en personas con arteriosclerosis cerebral. El presente estudio demuestra que existe una correlación positiva significativa entre la reactividad arterial retinal en un lado, y la reactividad de la circulación cerebral en el otro. Este hallazgo significa que arteriosclerosis suficientemente severa para afectar determinaciones de esta naturaleza es capaz de implicar los vasos retinales y cerebrales a la vez.

REFERENCES

[1] Alpers, B. J., Forster, F. M., and Herbut, P. A.: Retinal, cerebral, and systemic arteriosclerosis: A histopathologic study. Arch. Neurol. & Psychiat. **60:** 440, 1948.

[2] SIEKER, H. O., AND HICKAM, J. B.: Normal and impaired retinal vascular reactivity. Circulation **7:** 79, 1953.

[3] SCHEINBERG, P.: Cerebral blood flow in vascular disease of the brain, with observations on the effect of stellate ganglion block. Am. J. Med. **8:** 139, 1950.

[4] SCHIEVE, J. F., AND WILSON, W. P.: The influence of age, anesthesia, and cerebral arteriosclerosis on cerebral vascular activity to CO_2. Am. J. Med. To be published.

[5] KETY, S. S., AND SCHMIDT, C. F.: The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations. Am. J. Physiol. **143:** 53, 1945.

[6] SCHEINBERG, P., AND STEAD, E. A., JR.: The cerebral blood flow in male subjects as measured by the nitrous oxide technique. Normal values for blood flow, oxygen utilization, and peripheral resistance, with observations on the effect of tilting and anxiety. J. Clin. Investigation **28:** 1163, 1949.

Effect of Neck Compression on Sodium Excretion in Subjects with Congestive Heart Failure

By THOMAS A. LOMBARDO, M.D., AND TINSLEY R. HARRISON, M.D.

Previous studies on normal subjects have shown that neck compression causes increased urinary excretion of sodium in the sitting position, but has little or no effect in the recumbent position. In the present study, patients with congestive heart failure have exhibited no increase in urinary sodium excretion after neck compression.

PREVIOUS studies[1, 2] have shown that the decline in sodium excretion which occurs in the sitting position, as compared with recumbency, can be partially but not completely prevented by compression of the neck. Neck compression of the same subjects in the horizontal and head-down (Trendelenburg) positions had little or no effect. Also, removal of small amounts of blood from sitting subjects caused reduction of sodium excretion which could be prevented by compression of the neck.[3] These observations were interpreted as indicating the existence of a central homeostatic mechanism which regulates the volume of extracellular fluid by altering sodium excretion, and is apparently activated by changes in the volume of body fluids rather than by changes in cardiac output. The present study was performed to learn whether such a mechanism is active in patients with congestive heart failure.

METHODS

Four patients in congestive heart failure were studied. None had recently received mercurial diuretics. Each subject came to the laboratory in the fasting state, and ingested 200 ml. of 0.14 per cent sodium chloride every 30 minutes. Urine was collected at hourly intervals for a period of nine hours, and one small chocolate bar was consumed every two hours. Serum sodium analyses were done at the beginning and end of the studies. These observations will be reported later.

Experiments dealing with compression of the neck were conducted in the same manner but were performed a few days later. A blood pressure cuff was wrapped around the subject's neck and sustained at a pressure of 20 mm. Hg.

Sodium analyses were done according to the method described by Mosher and co-workers[4] using the flame photometer.

RESULTS

Since the results were essentially similar for all four subjects, they are presented as averages in figure 1. For the purpose of comparison, similar observations made on normal subjects[2] are also presented.

Urine Volume. This function increased shortly after the subjects began to drink the dilute sodium chloride solution. Diuresis attained a peak at the end of the second hour in the normal subjects, but the congestive heart failure patients did not show maximal diuresis until the sixth hour. The total diuresis was much smaller in the patients exhibiting heart failure. After maximal diuresis was reached, the normals continued to excrete water in excess of intake, whereas the congestive heart failure subjects failed to do so.

Neck compression was not associated with significant alterations in urine volume of either group. The diuresis noted in the normal subjects is compatible with the studies of Verney,[5] who demonstrated inhibition of the posterior pituitary consequent to the ingestion of hypotonic solution. A lack of diuresis in the patients with heart failure was perhaps due to the presence of excessive amounts of an antidiuretic substance.[6]

Sodium Excretion. During the control studies,

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the normal subjects displayed a progressive rise in sodium output which soon exceeded the intake (fig. 1). On the contrary, the patients with conjestive heart failure were unable to excrete the sodium, and at no time did the

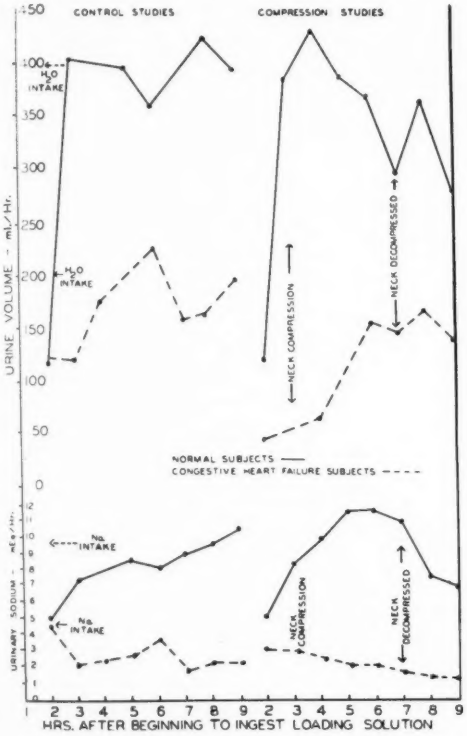

FIG. 1. The mean alterations in the renal excretion of water in four normal and four congestive heart failure subjects in the sitting position are presented in the upper left graph. The effect of neck compression (20 mm. Hg) on this same function on the same subjects appears on the upper right graph. The lower graphs represent the hourly excretion of sodium in the same subjects with and without neck compression. The normal subjects ingested 200 ml. of 0.14 per cent sodium chloride every hour, and the patients with congestive heart failure ingested 400 ml. of 0.14 per cent sodium chloride every hour.

output equal or exceed the intake. As the observations continued, a decline in sodium excretion was noted.

Compression of the neck in normal subjects produced a significant increment in sodium excretion which was maximal at the end of the second hour. This procedure failed to increase sodium excretion in subjects with heart failure.

The patients with congestive heart failure failed to exhibit increased sodium output when the neck was compressed in the sitting position. Normal subjects displayed this response in the sitting position but not in the horizontal position.[2] The reason for these variations is not clear at the present time. In any case the observations suggest either (1) that the postulated volume regulatory mechanism is inactive in patients with congestive failure, or (2) that if this mechanism is active, its effects are overshadowed by some more potent mechanism, tending to cause sodium retention.

SUMMARY

1. Neck compression, under conditions which cause significant increments in sodium excretion of normal subjects, failed to increase sodium excretion in four patients with congestive heart failure.

2. In patients with congestive failure, the previously postulated intracranial "volume center" concerned with the regulation of the volume of extracellular fluid appears to be either inactive or overshadowed by some more powerful mechanism favoring sodium retention.

3. Patients with congestive failure exhibited impairment of excretion, not only of sodium but also of water.

SUMARIO ESPAÑOL

Previos estudios en sujetos normales han mostrado qué compresión al cuello causa aumento en excreción de sodio en la posición sentada, pero tiene poco o ningún efecto en la posición recostada. En el presente estudio, pacientes en decompensación cardíaca no mostraron aumento en excreción de sodio después de compresión al cuello.

REFERENCES

[1] LEWIS, J. M., JR., BUIE, R. M., SEVIER, S. M., AND HARRISON, T. R.: The effects of posture and of congestion of the head on sodium excretion in normal subjects. Circulation **2:** 822, 1950.

[2] VIAR, W. N., OLIVER, B. B., EISENBERG, S., LOMBARDO, T. A., WILLIS, K., AND HARRISON, T. R.: The effect of posture and compression of

the neck on the excretion of electrolytes and glomerular filtration: Further studies. Circulation **3:** 105, 1951.

[3] LOMBARDO, T. A., EISENBERG, S., OLIVER, B. B., VIAR, W. N., EDDLEMAN, E. E., JR., AND HARRISON, T. R.: Effects of bleeding on electrolyte excretion and on glomerular filtration. Circulation **3:** 260, 1951.

[4] MOSHER, R. E., BOYLE, A. J., BIRD, E. J., JACOBSON, S. D., BATCHELOR, T. M., ISERI, L. T., AND MYERS, G. B.: The use of flame photometry for the quantitative determination of sodium and potassium in plasma and urine. Am. J. Clin. Path. **19:** 461, 1949.

[5] VERNEY, E. B.: Absorption and excretion of water; the antidiuretic hormone. Lancet **2:** 739, 781, 1949.

[6] BERCU, B. A., ROKAU, S. N., AND MASSIE, E.: Antidiuretic action of the urine of patients in cardiac failure. Circulation **2:** 409, 1950.

The Effect of Posture on the Excretion of Water and Sodium by Patients with Congestive Heart Failure

By THOMAS A. LOMBARDO, M.D.

Four patients with congestive heart failure were studied in the sitting and the recumbent positions. After hypotonic loading maximal diuresis set in at six hours, as compared with three hours in the normal subjects. Heart failure patients never excreted more than 50 per cent of water intake in either position. Likewise, these patients never equalled sodium intake with urinary excretion of sodium. Sodium excretion in the two positions was approximately the same. Increase in venous pressure, lengthening of circulation time, decline of vital capacity, and decline of serum sodium concentration were noted after each investigation period. These results are interpreted as indicating that the previously postulated intracranial volume regulating center is either inactive or overpowered by a more powerful mechanism in the patient with congestive heart failure.

A NUMBER of recent investigations have been concerned with the possible relationship between alterations in fluid volume and sodium excretion. Thus studies on normal subjects[1, 2] have shown that the decline in sodium excretion which occurs in the sitting position, as compared with recumbency, can be partially but not completely prevented by compression of the neck. Also, removal of small amounts of blood from sitting subjects caused reduction of sodium excretion which could be prevented by compression of the neck.[3] These observations were interpreted as indicating the existence of a central homeostatic mechanism concerned in regulating the volume of body fluids. The finding of hypernatremia and hyperchloremia with little or no salt excretion in the urine of patients with brain damage[4] indicates that a center in the brain may exist, which responds to tonicity changes. Furthermore, Lewy and Gassman[5] have produced hyperchloremia and hyperchloruria, but not polyuria, in cats by inducing lesions in the paraoptic nuclei.

Welt and Orloff[6] have shown that increases in plasma volume as much as 51 per cent, using salt-poor albumin, are not associated with increase in the renal excretion of sodium. Recently, Strauss and co-workers[7] have shown that hypotonic expansion of the extracellular fluid in normal recumbent subjects is uniformly effective in augmenting the renal excretion of sodium, without changes in creatinine clearance. However, no effect was observed in the sitting position. These data were interpreted as indicating that an increase in extracellular fluid volume in the cephalic portion of the body produces an increase in sodium excretion. Conversely, a contraction of extracellular volume in the cephalad portion of the body may be a stimulus for sodium retention. On the other hand the data indicate that changes in total plasma volume[6] and total extracellular volume[7] are without effect unless associated with corresponding local changes in the cephalic portion of the body.

Since neck compression fails to increase sodium excretion in sitting patients with congestive heart failure,[8] it is possible that the postulated volume regulatory mechanism is inactive in such patients, or that if the mechanism is active, its effects are overshadowed by some more potent mechanism tending to cause sodium retention. In order to test the hypothesis, it was decided to study the effect of posture on sodium excretion in patients with congestive heart failure.

METHODS

Four patients in congestive heart failure were studied on separate days, in the sitting and recum-

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Aided by a grant from the Life Insurance Medical Research Fund.

bent positions. Dietary control was not attempted, and none of the patients had recently received mercurial diuretics. Each subjects came to the laboratory in the fasting state and ingested 200 ml. of 0.14 per cent sodium chloride solution every 30 minutes. Similar observations on normal subjects ingesting 200 ml. of 0.14 per cent sodium chloride solution every hour in the recumbent position, and 400 ml. of the same solution in the sitting position have been reported.[2]

Urine was voided and collected every hour for a nine-hour period, and one small chocolate bar was consumed every two hours. Ten milliliters of blood were drawn at the beginning and the end of each study. Also, venous pressure (saline manometers at right heart level), vital capacity, and circulation time (arm-to-tongue-Decholin) were measured at the beginning and the end of the observations. Serum analysis for sodium was done according to the method described by Mosher and associates,[9] using the flame photometer.

Results

Since all four subjects showed the same directional changes in both the sitting and the recumbent positions, the results are presented as averages in figure 1. For the purpose of comparison, similar observations made on normal subjects[2] are also presented.

Urine Volume in the Sitting and Recumbent Positions. In both the sitting and the recumbent positions, urinary output increased shortly after the subjects began to ingest the dilute sodium chloride solution. Observations in the sitting position revealed that the normal subjects attained maximal diuresis at the end of the third hour, whereas, the patients with congestive heart failure did not show maximal diuresis until the sixth hour (fig. 1). After the peak of diuresis was reached, the normal subjects continued to excrete water in excess of intake, but the congestive failure subjects failed to do so. Even though the intake was the same for both groups in the sitting position, the patients with congestive failure retained an average of approximately 50 per cent of the water ingested.

Although the water intake of the recumbent patients with congestive failure was twice as great as the normal subjects in the same position, urine volume was considerably less. The normal recumbent subjects excreted a volume greater than their intake, in contrast to the subjects with congestive heart failure who excreted less than 50 per cent of their intake. No significant differences in total volume output were noted in the subjects with heart failure in the recumbent as compared with the sitting position. However, maximal diuresis was reached at the end of the fourth hour in the recumbent position, and at the end of the sixth hour in the sitting position.

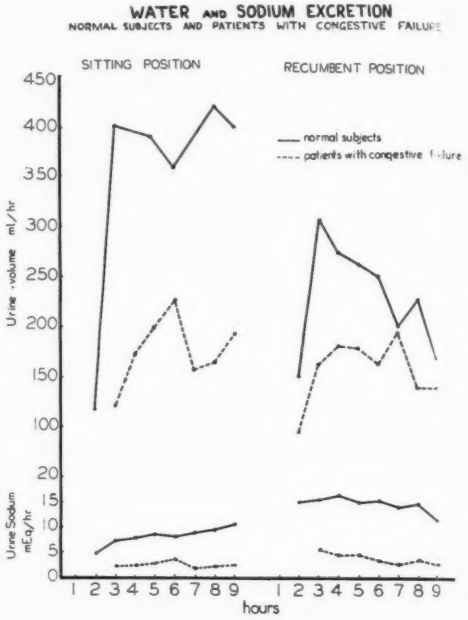

FIG. 1. Mean alterations in the renal excretion of water and sodium in the sitting and recumbent positions in four normal subjects and four subjects with congestive heart failure. In the sitting position both groups ingested 200 ml. of 0.14 per cent sodium chloride every 30 minutes. However, in the recumbent position, the normal subjects ingested only 200 ml. of the same solution every hour, but the congestive heart failure patients ingested twice as much. Thus, in the sitting position the intake of sodium was approximately 10 mEq. per hour. The intake was the same in the recumbent patients with congestive failure. The recumbent normal subjects ingested approximately 5 mEq. of sodium per hour.

The normal subjects displayed an initial positive balance of sodium while sitting and a definite negative balance while recumbent. They soon reached approximate equilibrium as regards water. The patients with congestive failure displayed markedly positive balances of water and sodium in both positions. (See text.)

Sodium Excretion in the Sitting and the Recumbent Positions. Studies in the sitting position revealed that normal subjects displayed a progressive rise in sodium output which almost equalled their intake. On the contrary, the patients with congestive heart failure were unable to excrete significant amounts of sodium, and at no time did the output equal or exceed the intake (fig. 1).

In the recumbent position, the subjects with heart failure ingested twice as much sodium as the normals. In spite of this, sodium excretion was much greater in the normal subjects. The normal subjects exhibited a greater output of sodium in the recumbent as compared with the sitting position, but the congestive heart failure subjects failed to show this response to a significant degree (fig. 1).

Serum Sodium Content. On both days of the observations, the serum sodium content averaged 139.0 mEq. per liter in the four subjects before ingesting the dilute sodium chloride solution. An average decline in serum sodium of 6.6 mEq. per liter was noted at the end of the sitting studies. This represents a 5 per cent decline in serum sodium concentration (table 1).

In the recumbent position, an average decline in serum sodium was 5.5 mEq. per liter after ingesting the hypotonic solution or a 4 per cent decline (table 1). Therefore, the fall in serum sodium concentration occurring with the ingestion of hypotonic saline did not differ significantly in the sitting and recumbent positions.

Venous Pressure, Circulation Time, and Vital Capacity. The average venous pressure observed before beginning the sitting and recumbent studies was 233 and 224 mm. H_2O, respectively. After ingesting the dilute saline solution in the sitting position, the average rise in venous pressure was 61 mm. H_2O, or a 27 per cent increase. An average rise of 33 mm. H_2O was noted after ingesting the dilute solution while in the recumbent position. This rise represents 19 per cent increase above the level before commencing the study. All subjects demonstrated a rise in venous pressure at the end of the sitting and recumbent observations (table 1).

After ingesting the dilute saline solution, the arm-to-tongue (Decholin) circulation time increased by an average of five seconds in the sitting position and by 28 seconds in the recumbent position. At the same time the vital capacity declined under both conditions studied. The average decline in the vital capacity was 300 and 400 ml. in the sitting and recumbent positions, respectively (table 1).

TABLE 1.—*Effects in Subjects with Congestive Heart Failure of Ingesting 3600 ml. of Hypotonic Saline Solution During Nine Hours*

Subject		Serum Sodium mEq./L.	Venous Pressure mm. H_2O	Circulation Time arm-to-tongue (Decholin)	Vital Capacity liters
Sitting Position					
J.A.	Before	143.5	190	35	2.5
	After	135.0	265	35	2.1
B.M.	Before	135.0	310	70	3.1
	After	128.0	410	75	3.0
C.H.	Before	139.0	240	25	3.0
	After	132.0	260	30	2.7
C.W.	Before	138.0	190	20	2.5
	After	134.0	240	30	2.2
Recumbent Position					
J.A.	Before	133.0	165	28	2.8
	After	129.0	250	44	2.0
B.M.	Before	136.0	410	43	2.8
	After	129.0	426	125	2.6
C.H.	Before	141.0	160	25	3.0
	After	138.0	170	30	2.8
C.W.	Before	143.5	160	25	2.5
	After	135.5	180	35	2.2

DISCUSSION

The patients differed from normal persons subjected to the same procedures in several significant respects: (1) They exhibited a strikingly positive balance both for sodium and water, in both the recumbent and sitting positions. (2) They developed a well-marked decline in the sodium concentration of extracellular fluid. (3) There was relatively little difference between the two positions as regards sodium output; normal subjects excrete a significantly greater amount of sodium when recumbent. (4) Within the course of several hours significant prolongation of circulation

time, elevation of venous pressure, and reduction of vital capacity, occurred as a consequence of retention of fluid during the procedure.

These observations furnish additional evidence for the concept that retention of water by patients with congestive failure is not necessarily secondary to sodium retention, but tends to occur independently. This confirms the observations of Fremont-Smith[10] and of Miller.[11] The observations indicate that the normal delicate homeostatic mechanisms regulating sodium and water excretion are gravely disturbed in patients with congestive failure. It has been previously shown[8] that such patients do not display the usual increase in sodium excretion produced by compression of the neck. The present study indicates an absent or impaired effect of posture, and also an inability of these patients to prevent significant osmolar dilution when hypotonic saline is ingested. The observations can perhaps be explained by the assumption that there is some powerful mechanism, active in subjects with heart failure, but absent (or inactive) in normal subjects, and tending to overcome the normal delicate adjustments to changes in posture, to alterations in intracranial fluid volume, and to slight changes in osmolar concentration. The nature of such a mechanism, if it actually exists, is obscure at the present time and can only be elucidated by further investigations.

Summary

1. Patients with congestive heart failure ingesting hypotonic solution of sodium chloride displayed relatively greater retention of water than of sodium and developed significant decline in serum sodium. It is believed that such subjects have primary as well as secondary (to sodium) water retention.

2. The effect of posture on the excretion of sodium and of water is absent or markedly diminished in patients with congestive heart failure as compared with normal subjects. The previously postulated intracranial volume regulating mechanism appears to be inactive or overshadowed in such subjects.

Sumario Español

Cuatro pacientes con decompensación cardiaca fueron estudiados en posición sentada y reclinada. Después de haber sido cargados hipotonicamente la diuresis comenzó a las seis horas, comparado con tres horas en sujetos normales. Pacientes con decompensación cardiaca nunca eliminaron mas de 50% del agua ingerida en ninguna posición. De igual manera, estos pacientes nunca igualaron la cantidad de sodio consumida a la cantidad eliminada en la orina. Excreción de sodio en las dos posiciones fué aproximadamente igual. Aumento en la presión venosa, prolongación del tiempo de circulación, diminución de la capacidad vital y diminución en la concentración del sodio en el suero fueron observados luego de cada período de investigación. Estos resultados han sido interpretados como indicativos de que el postulado centro intracranial de volumen o es inactivo o subyugado a un mecanismo mas poderoso en el paciente con decompensación cardiaca.

References

[1] Lewis, J. M., Jr., Buie, R. M., Sevier, S. M., and Harrison, T. R.: The effects of posture and of congestion of the head on sodium excretion in normal subjects. Circulation **2:** 822, 1950.

[2] Viar, W. N., Oliver, B. B., Eisenberg, Seymour, Lombardo, T. A., Willis, Kathryn, and Harrison, T. R.: The effect of posture and of compression of the neck on the excretion of electrolytes and glomerular filtration: further studies. Circulation **3:** 105, 1951.

[3] Lombardo, T. A., Eisenberg, Seymour, Oliver, B. B., Viar, W. N., Eddleman, E. E., Jr., and Harrison, T. R.: Effects of bleeding on electrolyte excretion and on glomerular filtration. Circulation **3:** 260, 1951.

[4] Abbott, E. N.: Sodium and chloride retention without renal disease. Lancet **1:** 1035, 1939.

[5] Lewy, F. H., and Gassmann, F. K.: Experiments on the hypothalmic nuclei in the regulation of chloride and sugar metabolism. Am. J. Physiol. **112:** 504, 1935.

[6] Welt, L. G., and Orloff, J.: The effects of an increase in plasma volume on the metabolism and excretion of water by normal subjects. J. Clin. Investigation **30:** 751, 1951.

[7] Strauss, M. B., Davis, R. K., Rosenbaum, J. D., and Rossmeisl, E. G.: Production of increased renal sodium excretion by hypotonic expansion of extracellular fluid volume in recum-

lent subjects. J. Clin. Investigation **31:** 80, 1952.

[8] LOMBARDO, THOMAS A., AND HARRISON, T. R. Effect of neck compression on sodium excretion in subjects with congestive heart failure. Circulation **7:** 88, 1953.

[9] MOSHER, R. E., BOYLE, A. J., BIRD, E. J., JACOBSON, S. D., BATCHELOR, T. M., ISERI, L. T., AND MYERS, G. B.: The use of flame photometry for the quantitative determination of sodium and potassium in plasma and urine. Am. J. Clin. Path. **19:** 461, 1949.

[10] FREMONT-SMITH, FRANK: The mechanism of water diuresis in man. Proc. Soc. Clin. Investigation. **9:** 7, 1930.

[11] MILLER, G. E.: Water and electrolyte metabolism in congestive heart failure. Circulation **4:** 270, 1951.

The Urinary Output of Catechol Derivatives Including Adrenaline in Normal Individuals, in Essential Hypertension, and in Myocardial Infarction

By FRANKLIN R. NUZUM, M.D., AND FRITZ BISCHOFF, PH.D.

Based on Shaw's specific test, the adrenaline content of the urine of some normal individuals was considerably higher than has been reported by those using the von Euler technic (adsorption at an alkaline pH, elution and bioassay). One patient with myocardial infarction showed highly significant amounts on four occasions. The marked elevation in the Kroneberg-Schümann catechol ratio for hypertension patients as compared with normals, reported by these authors, was not confirmed by our findings. In three cases of myocardial infarction the ratio was elevated. Our ratios for normals confirm the original work.

WHILE hypotension results following the removal of the adrenals, tumors of this gland frequently produce hypertension. One specific type of tumor, pheochromocytoma, gives rise to two types of hypertension, of which one is paroxysmal in character and due to liberation into the blood stream of excessive amounts of adrenaline. Pheochromocytoma also in some instances results in a progressive type of sustained hypertension, which is indistinguishable from essential hypertension.[1] At the moment, the consensus is that essential hypertension is not concerned with the adrenal medulla, but Perera states,[2] "The possibility must still be entertained that sensitization of blood vessels to normal amounts of norepinephrine would account for hypertension, and that we are not entitled as yet to eliminate the adrenal medulla from further consideration." Bing[3] has hinted at a relation of dihydroxyphenylalanine to essential hypertension, in which there is decarboxylation to a pressor amine in an ischemic kidney, which cannot deaminate. There is much indirect evidence that adrenaline and noradrenaline are formed from phenylalanine.[4] The catechol nucleus is formed by oxidation, and removal of the carboxyl group is brought about by enzymatic decarboxylation. The nonphenolic sympathomimetic amines appear to be destroyed in the body by deamination, but conjugation appears to be the principal mode of inactivation of phenolic sympathomimetic amines. Adrenaline administered orally is recovered in the urine as a conjugated phenol sulfate.[5, 6] In the rat conjugation of the amino group of ephedrine has been demonstrated.

Attempts to determine the concentration of adrenaline in mammalian blood either by pharmacologic or microchemical methods have been initiated at intervals over the last 30 years.[7-13] In spite of the concentrated and ingenious efforts made, the status of the problem, as far as human blood is concerned, is still controversial. Shaw[9] and Gaddum and Schild[14] developed respectively microchemical and fluorescence methods which are highly sensitive and accurate as far as pure adrenaline is concerned, but the application of these methods to blood with the complications of interfering substances, instability, and recovery has in our opinion not been satisfactorily solved. Our interest in the problem, integrated with the disappointment of some past experience in trying to determine blood adrenaline, was shifted to urine following the report of Kroneberg and Schümann.[15]

According to these authors the blood pressure raising fraction of human urine, originally called

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"urosympathin," behaves pharmacologically as noradrenaline; the content of this substance in the urine of patients with essential hypertension and the hypertension of chronic nephritis is raised over the level of normals, and in hypertension patients there is a marked elevation of a conjugated pyrocatechol fraction related to noradrenaline which may be liberated by acid hydrolysis. To determine this fraction the Shaw microcolorimetric method, which depends upon the catalytic reduction of arsenomolybdic acid to a blue colored compound by adrenaline like compounds, was used.

Plan

The present study was an attempt to verify the findings of Kroneberg and Schümann that the conjugated catechol fraction of human urine is markedly raised in hypertension. These authors do not give the details of their application of the Shaw principle to their problem. As these details may well be of considerable importance, we have recorded our experimental procedure in detail. Shaw found that if adrenaline in solution is pretreated with alkali the color development in his test is increased fivefold. This phenomenon is characteristic for adrenaline and is not observed for catechol, noradrenaline, and others. Unfortunately Kroneberg and Schümann do not mention whether they used the specific or nonspecific Shaw test. In our experiments we used both procedures.

The present study concerns the determination of adrenaline and the catechol fraction in the urine of 17 normal individuals, in 17 patients with well established essential hypertension, and in eight patients with angina pectoris and myocardial infarction.

The ages in each of these groups of private patients averaged from 45 to 68 years. Those with essential hypertension had been followed from 2 to 22 years, and the pressures recorded in the tables were the average of many readings taken over a period of months or years. Four patients were experiencing severe anginal bouts and four were recovering from recent myocardial infarctions. The patients in all four groups were hospitalized during this study.

In recording the data in tables 1 and 2, content was calculated in milligrams per 12 hours as catechol equivalents for the nonspecific and specific tests and for the ratios of these concentrations before and after hydrolysis. In all these categories catechol or crystalline adrenaline (Parke, Davis and Co.) not pretreated with alkali was used as the standard. When the color equivalent of the unknowns after alkali treatment was elevated, indicating the presence of adrenaline, the adrenaline content was estimated from the color ratios obtained with adrenaline standards processed according to the specific and nonspecific Shaw tests. Since the color derived from catechol is slightly decreased on prealkali treatment and that of adrenaline greatly increased, a proper ratio of these two substances could produce a compensating result; the response for noradrenaline is unchanged.

Methods

Method for Urinary Catechol Derivatives. 1. Dilution depends on original volume, depth of color, clarity, and so forth, of the specimen, and varied from 1 to 16 to 1 to 96. In each of four 50 ml. flasks place 0.25 cc. of concentrated sulfuric acid. Add to each of two flasks 12.5 cc. of diluted urine, to the third flask add 12.5 cc. of a 2 γ* per cubic centimeter solution of adrenaline, and to the fourth flask add 12.5 cc. double distilled water. Place one flask with urine in boiling water bath 15 minutes to hydrolyze.

2. To each of the four flasks add 0.8 cc. 30 per cent sodium hydroxide and 0.9 cc. normal sodium acetate, (pH 4.0). Fill to the 50 cc. mark with water. Mix. From each flask pipet 2 cc. samples in each of two centrifuge tubes. Add to each tube 3 cc. water and 1 cc. of Shaw's[9] aluminum hydroxide suspension. Centrifuge seven minutes at 2700 revolutions per minute. Place supernatant fluids in clean centrifuge tubes containing 1 cc. aluminum hydroxide suspension, and add to each 3 cc. ammonium chloride-sodium hydroxide buffer† (pH 8.3). Centrifuge three minutes. Discard supernatants. Wash precipitates with 3 cc. buffer; centrifuge three minutes; discard supernatants.

3. Add to each tube 3 cc. water. To four tubes add 0.9 cc. 4 per cent sodium hydroxide for Shaw's specific test and to the four corresponding tubes 0.9 cc. sulfuric acid (approximately 1/6 normal). Mix.

Add to each tube 2 cc. of Shaw's sulfurous acid reagent, 0.75 cc. arsenomolybdic acid reagent, mix and place tubes in boiling water bath for five min-

* γ is used in this paper to indicate .001 mg.

† Ammonium chloride–sodium hydroxide buffer: 17.38 Gm. ammonium chloride and 1 Gm. sodium hydroxide in 300 cc. water, pH 8.37.

utes. Cool. After at least 20 minutes read colors in colorimeter. The adrenaline standard corresponds to 1 γ. The increase in color upon alkali treatment is about sixfold.

The reagents used were prepared according to Shaw's directions.[9]* The ammonium chloride buffer was introduced to eliminate the use of phenolphthalein which may produce a high blank.

The recovery of adrenaline in a concentration of 0.05 γ per cubic centimeter run through the Shaw method was found to be at best, 56 per cent. Upon using a greater amount, 0.25 γ adrenaline per cubic centimeter, the recovery was more nearly quantitative. The recoveries for two 4 γ standards of catechol were 84 and 83 per cent.

In comparing a standard of 4 γ catechol against the 1 γ adrenaline standard, 1 γ catechol had the color equivalent of 0.25 γ adrenaline in the acidic tests. In the alkaline test for catechol, 1 γ has the equivalent of 0.20 γ adrenaline in the acid test. A standard of 4 γ catechol was adopted to replace the adrenaline standard originally used. The greater stability and availability of catechol made this substitution desirable.

There is apparently no loss upon hydrolysis (boiling for 15 minutes with sulfuric acid) of either 2 γ per cubic centimeter adrenaline or 4 γ per cubic centimeter of catechol, since the minor color differences given by the hydrolyzed and unhydrolyzed standards were within the error inherent in the method (about 15 per cent).

Results and Discussion

There is no increase in the ratio of the catechol derivatives of hydrolyzed to unhydrolyzed urine in the hypertension group as compared with the normal group. (See table 1.) All the mean ratios, approximately 2.0, agree within once the standard deviation of the mean. Moreover, there are no individual ratios in the hypertension group above the highest individual ratios in the normal group. We have taken the liberty to calculate a mean and standard deviation of the mean for Kroneberg and Schümann's 10 normals; the result 1.73 $\pm$ 0.16 agrees well with our normal group. It is difficult to reconcile the discrepancy between their and our results for the hypertension group. Kroneberg and Schümann report ratios ranging from 2.0 to 9.5 for this series. We have pooled

* Since a number of the reagents used in this test are dangerous or highly poisonous, persons who have not had the proper training to handle such reagents should not attempt to prepare the reagents or run the test.

Table 1.—*Data on Individuals for the Kroneberg-Schümann Catechol Test and the Shaw Adrenaline Test*

Case and Sex	Diagnosis	12 Hour Urine	Ratios			Adrenaline
			Acid Tests, Hydrolyzed: Unhydrolyzed Urine	Hydrolyzed Urine, Alkaline: Acid Test	Unhydrolyzed Urine, Alkaline: Acid Test	Mg. in 12 Hours
K. J.	Normal	D	2.04	1.12	0.89	
m		N	1.97	1.00	1.00	
B. C.	Normal	D	1.94	0.96	0.84	
m		N	2.02	1.09	0.95	
D. S.	Normal	N	2.12	1.26	1.11	0.59
m						
V. D.	Normal	D	2.11	1.08	1.07	
f		N	2.48	1.30	0.93	0.30
G. H.	Normal	N	1.99	1.03	0.97	
f						
M. B.	Normal	D	1.63	1.04	0.90	
f		N	2.18	1.04	0.96	
M. R.	Normal	D	2.38	1.19	0.91	0.20?
f		N	1.77	1.04	0.89	
J. W.	Normal	D	2.20	1.18	1.39	0.78?
f	Asthma	N	1.50	1.20	0.85	0.90
L. A.	Normal	D	1.17	1.35	1.10	0.75
f		N	1.84	0.96	1.00	
M. B.	Normal	D	2.63	1.13	0.93	0.60
f		N	2.62	0.96	0.95	
M. B.	Normal	D	2.56	1.07	0.93	
f		N	1.66	0.98	1.02	
F. W.	Normal	N	1.76	0.96	0.85	
f		N	1.96	1.02	0.96	
A. B.	Normal	N	1.56	1.10	1.02	
f						
M. D.	Normal	D	1.67	1.00	0.89	
f		N	2.34	1.09	1.11	

TABLE 1—*Continued*

Case and Sex	Diagnosis	12 Hour Urine	Ratios: Acid Tests, Hydrolyzed: Unhydrolyzed Urine	Ratios: Hydrolyzed Urine, Alkaline: Acid Test	Ratios: Unhydrolyzed Urine, Alkaline: Acid Test	Adrenaline: Mg. in 12 Hours
M. B.	Normal	D	2.64	1.19	1.87	
f		N	2.07	0.91	1.08	
A. W.	Normal	D	1.96	1.02	0.94	
f		N	1.88	1.14	0.89	0.18?
E. L.	Normal	D	2.14	1.00	1.09	
f		N	2.15	1.52	1.01	1.13
R. P.	Mild hypertension	D	1.56	0.94	1.00	
m	180/90	N	1.60	1.05	0.87	
H. R.	Marked hypertension	D	1.64	1.07	1.02	
m	220/120	N	2.45	1.03	1.00	
E. F.	Marked hypertension	D	2.24	1.17	1.17	0.47
m	220/120	N	1.74	1.09	1.22	
G. B.	Hypertension	D	1.51	0.98	1.20	
m	165/94	N	1.67	0.86	1.11	
H. R.	Marked hypertension	D	2.13	0.98	1.10	
m	240/120	N	1.80	1.05	0.95	
F. S.	Hypertension	D	2.20	1.06	2.03	2.22?
m	190/70	N	1.75	1.02	0.69	
J. S.	Hypertension	D	2.41	0.73	1.54	1.04
m	176/108	N	1.14	1.17	1.07	0.52?
E. L.	Hypertension	D	1.73	1.16	1.02	0.27
m	165/80	N	2.17	1.15	1.07	0.21
E. M.	Marked hypertension	D	1.81	0.96	0.98	
m	220/120					
G. C.	Hypertension	D	1.67	0.82	0.90	
m	160/75					
J. H.	Marked hypertension	D	2.00	0.96	1.12	
m	240/120					

TABLE 1—*Continued*

Case and Sex	Diagnosis	12 Hour Urine	Ratios: Acid Tests, Hydrolyzed: Unhydrolyzed Urine	Ratios: Hydrolyzed Urine, Alkaline: Acid Test	Ratios: Unhydrolyzed Urine, Alkaline: Acid Test	Adrenaline: Mg. in 12 Hours
M. T.	Hypertension	D	1.81	1.11	0.92	
f	190/120	N	2.10	1.15	1.05	
E. B.	Hypertension	D	2.18	1.09	0.97	
f	218/110	N	1.71	1.10	0.77	
J. B.	Hypertension	D	2.21	1.13	1.04	
f	160/110	N	2.43	0.95	0.94	
L. B.	Hypertension	D	1.79	0.99	1.03	
f	154/100	N	2.00	0.88	0.89	
M. L.	Hypertension	D	1.84	1.38	1.26	0.44?
f	155/100					
C. M.	Hypertension	D	1.62	1.01	1.16	
f	190/115	N	2.16	0.90	1.07	
S. S.	Angina pectoris	D	1.84	1.01	1.06	
m	176/105	N	1.99	1.17	0.87	0.33?
A. R.	Myocardial infarction	D	2.69	0.82	1.10	
m	165/100	N	3.16	1.18	0.97	1.12
W. J.	Myocardial infarction	D	2.25	1.00	1.04	
m	158/110	N	3.28	1.03	1.00	
R. R.	Myocardial infarction	D	2.10	1.15	1.03	0.23
m	Angina pectoris 130/80	N	2.89	1.45	1.05	1.68
R. R.	(Repeat test)	24 hr.	3.49	1.10	1.69	0.44 24 hr.
m						
W. B.	Myocardial infarction	D	1.84	1.10	1.19	
m	170/110	N	1.29	0.77	0.65	
B. R.	Myocardial infarction	D	1.37	0.94	0.72	
m		N	1.85	0.94	0.94	
R. R.	(Repeat test)	24 hr.	2.45	1.26	1.14	0.79 24 hr.

TABLE 1—*Concluded*

Case and Sex	Diagnosis	12 Hour Urine	Ratios			Adrenaline
			Acid Tests, Hydrolyzed: Unhydrolyzed Urine	Hydrolyzed Urine, Alkaline: Acid Test	Unhydrolyzed Urine, Alkaline: Acid Test	Mg. in 12 Hours
E. N.	Myocardial infarction	D	1.59	1.31	1.35	
f	Angina pectoris 180/110	N	1.69	1.02	1.14	
M. T.	Angina pectoris	D	2.14	1.06	1.03	
f	188/120	N	2.02	1.16	1.20	0.22?

eight patients, with either angina pectoris or recent myocardial infarction. As a group, the mean index does not deviate from the normal. (See table 2.) However, in three cases of myocardial infarction the ratios 3.16, 3.28, and 3.49 must be considered abnormally high. (See table 1.)

established. In the hypertension group, two urines showed adrenaline in amounts of 0.47 and 0.3 mg. Doubtfully significant values were 2.2, 1.0, and 0.44 mg. On first glance it might appear paradoxic that a value of 2.2 is of doubtful significance, while a value of 0.3 is significant. The reason is that the dilution in one case was not in a range assuring the maximum analytic accuracy. In the heart cases there were two patients with well established amounts of adrenaline in the urine, one of which showed 0.2, 1.7, 0.44, and 0.79 mg. on four separate occasions. Since Kroneberg and Schümann believe the blood pressure-raising fraction in urine behaves pharmacologically as noradrenaline, our findings of the presence of adrenaline or a compound giving the adrenaline color reaction is of interest.

Goldenberg[16] states that the quantities of noradrenaline and adrenaline encountered in normal urine are too small to be determined by chemical means. It is true that the amounts detected by bioassay following von Euler and Luft's procedure[17] would be too small to detect by Shaw's method. Goldenberg also points out

TABLE 2.—*Means of Kroneberg-Schümann Catechol Ratios and of Shaw Specific Test Adrenaline Ratios (for Human Urines Under Various Conditions)*

Subjects	Acid Tests Hydrolyzed Urine: Unhydrolyzed Urine		Hydrolyzed Urine Alkaline Test: Acid Test		Unhydrolyzed Urine Alkaline Test: Acid Test		Mg. as Catechol Acid Test Hydrolyzed Urine	
	Day	Night	Day	Night	Day	Night	Day	Night
Normal, 17	2.06 ± 0.11	2.01 ± 0.07	1.09 ± 0.03	1.10 ± 0.04	1.04 ± 0.07	0.98 ± 0.02	62 ± 10	46 ± 7
Hypertension, 17	1.90 ± 0.07	1.89 ± 0.09	1.04 ± 0.04	1.03 ± 0.03	1.14 ± 0.07	0.98 ± 0.04	72 ± 12	56 ± 9
Heart condition, 8	1.98 ± 0.15	2.27 ± 0.26	1.05 ± 0.05	1.09 ± 0.07	1.07 ± 0.06	0.98 ± 0.06	64 ± 15	87 ± 22

Of the 17 normals, five patients showed amounts of adrenaline in the urine, based on the difference between Shaw's specific and nonspecific tests, which differences were significantly greater than the inherent experimental error of the method. The values in milligrams per 12 hours were: 0.3, 0.9, 0.75, 1.13, and 0.6. Three other urines produced doubtfully significant values. The fact that the mean ratios for the alkaline to acid tests were above 1.00 is indicative of the presence of some adrenaline. However, with an experimental error of 15 per cent and the dilutions required for the test, the presence of adrenaline in all urines was not

that adrenaline is easily oxidized at pH 7 when exposed to the air. Since the von Euler technic uses Shaw's aluminum hydroxide resorption at pH 8, there is probably a destruction of pharmacologic action, although the oxidation product still gives the chemical test. It would appear to us that since the instability of adrenaline at a pH more alkaline than 7 is well known, any bioassay method which uses an extract which has been above this pH is open to criticism.

The only substance beside adrenaline known to give Shaw's specific test is *p*-sympatol, and this in a concentration 2000 times that of adrenaline. While it might seem presumptuous

that we should report values for adrenaline so at variance with the bioassay tests obtained by the von Euler method, we cannot dismiss as an artefact the consistant differences obtained between Shaw's acid and alkaline procedure. Rather we feel that in the light of the discrepancy of the two procedures, further investigation is warranted. Kroneberg and Schümann originally suggested that the bases might be so altered in the urine as to still give the chemical test after the products no longer initiated pharmacologic action.

Summary

Based on Shaw's specific test, adrenaline was found in the urine of normal subjects, patients with hypertension, and patients with myocardial infarction. The accuracy of the method was not sufficient to establish the presence of adrenaline in all urines. Two patients with myocardial infarction showed highly significant amounts of adrenaline and one of these showed such amounts on four occasions. These findings have not been previously reported and the possibility of an etiologic relationship between an increased amount of adrenaline and myocardial infarction is intriguing.

Kroneberg and Schümann's ratio of catechol derivatives in hydrolyzed and unhydrolyzed urine was confirmed for a group of 17 normals. The marked elevation in ratio observed for hypertension patients by these authors was not confirmed by our findings. However, in three patients with myocardial infarction, a significantly elevated ratio was observed.

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Sumario Español

Basado en la prueba específica de Shaw, el contenido de adrenalina en la orina de algunos sujetos normales fué considerablemente más alto que lo que se ha reportado por aquellos que usan la técnica de von Euler (absorción a un pH alkalino, levigación y bioensayo). Un paciente con infarto del miocardio mostró cantidades altas significativas en cuatro ocasiones. La marcada elevación en la proporción Kroneberg-Schumann de catecol en pacientes hipertensos comparado con sujetos normales, reportado por estos autores, no fué confirmada por nuestros hallazgos. En tres casos de infartos del miocardio la proporción estuvo elevada. Nuestras proporciones para normales confirma el trabajo original.

References

[1] Green, D. M.: Pheochromocytoma and chronic hypertension. J.A.M.A. **131:** 1260, 1946.

[2] Perera, G. A.: Endocrine factors in hypertension. Bull. New York Acad. Med. **28:** 43, 1952.

[3] Bing, R. J.: The formation of hydroxytyramine by extracts of renal cortex and by perfused kidneys. Am. J. Physiol. **132:** 497, 1941.

[4] Beyer, K. H.: Sympathomimetic amines. Physiol. Rev. **26:** 169, 1946.

[5] Richter, D., and MacIntosh, F. C.: Adrenaline ester. Am. J. Physiol. **135:** 1, 1941.

[6] Beyer, K. H., and Shapiro, S. H.: The excretion of conjugated epinephrine related compounds. Am. J. Physiol. **144:** 321, 1945.

[7] Stewart, G. N., and Rogoff, J. M.: Quantitative experiments on liberation of epinephrine from the adrenals after section of their nerves, with special reference to the question of indispensability of epinephrine for the organism. J. Pharmacol. **10:** 1, 1917.

[8] Whitehorn, J. C.: A chemical method for estimating epinephrine in blood. J. Biol. Chem. **108:** 633, 1935.

[9] Shaw, F. H.: The estimation of adrenaline. Biochem. J. **32:** 19, 1938.

[10] Bloor, W. R., and Bullen, S. S.: The determination of adrenalin in blood. J. Biol. Chem. **138:** 727, 1941.

[11] Raab, W.: Adrenaline and related substances in blood and tissues. Biochem. J. **37:** 470, 1943.

[12] Jorgensen, K. S.: Studies on the quantitative determination of the adrenaline content of the blood with the fluorescence method. Acta Pharmacol. **1:** 225, 1945.

[13] West, G. B.: Quantitative studies of adrenaline and noradrenaline. J. Physiol. **106:** 418, 1947.

[14] Gaddum, J. H., and Schild, H.: A sensitive physical test for adrenaline. J. Physiol. **80:** 9 P, 1934.

[15] Kroneberg, G., and Schümann, H-J.: Urosympathin. Arch. exper. Path. u. Pharmakol. **209:** 350, 1950.

[16] Goldenberg, M.: Adrenal medullary function. Am. J. Med. **10:** 627, 1951.

[17] von Euler, U. S., and Luft, R.: The effect of adrenocorticotrophic hormone (ACTH) and adrenocorticotrophically active peptides (ACTH peptides) on the circulating eosinophiles and urinary excretion of adrenaline and noradrenaline in a human subject. Acta. endocrinol. **3:** 323, 1949.

Right Auricular and Ventricular Pressure Patterns in Constrictive Pericarditis

By Paul N. G. Yu, M.D., Frank W. Lovejoy, Jr., M.D., Howard A. Joos, M.D., Robert E. Nye, Jr., M.D., and Earl B. Mahoney, M.D.

The characteristic intracardiac pressure patterns of four patients with constrictive pericarditis are described. The significance of a high ratio between right ventricular end-diastolic and systolic pressure is demonstrated. Postoperative changes are described in one patient and the mechanism of the production of the pressure patterns is discussed.

PRESSURE patterns from the right auricle and ventricle in constrictive pericarditis were first described in 1946 by Bloomfield and associates[1] and recently by Hansen and associates[2] and McKusick.[3] The right auricular pressure curve consists of (*a*) an M or W shaped pattern with two upward and two downward deflections, (*b*) moderately or markedly elevated mean pressure and (*c*) failure of the downward deflections to reach the baseline. The right ventricular pressure curve consists of (*a*) a slightly elevated systolic pressure and (*b*) a rapid diastolic dip followed by a high diastolic plateau. These pressure patterns were considered diagnostic of constrictive pericarditis and disappeared in one case following successful pericardiectomy.[2] In the series of cases of constrictive pericarditis reported by McKusick,[3] no postoperative pressure tracings are available in patients who had obtained significant clinical improvement. In 1948 Wood and associates[4] thought that the pressure curves obtained from the right ventricle in one of their patients with constrictive pericarditis might be due to artifact but Hansen and associates and McKusick contended that the pressure patterns are characteristic of this disorder.

Clinical differentiation between constrictive pericarditis and other simulating conditions may be difficult. A correct diagnosis is of paramount importance, since constrictive pericarditis can be treated surgically; therefore, demonstration of characteristic pressure patterns by cardiac catheterization in constrictive pericarditis may prove an important diagnostic adjunct.

It is the purpose of this report (*a*) to describe and emphasize the various features of the pressure patterns in four patients with constrictive pericarditis and (*b*) to show the difference between preoperative and postoperative pressure curves in one patient. The significance of the ratio between right ventricular end-diastolic and systolic pressures is emphasized.

Method and Material

Cardiac catheterizations were performed as usual. The pressure tracings were recorded using a Statham strain gage. A Sanborn strain gage amplifier in a multichannel direct writing oscillograph* was used in most instances. The records also included a simultaneous registration of the pneumogram and electrocardiogram.

All pressures were recorded in millimeters of mercury above atmospheric pressure. The reference point for each patient was 6.5 cm. below the angle of Louis. The ventricular pressure tracings were measured for systolic and end-diastolic values in each heart beat during two respiratory cycles and the results averaged. The right ventricular and auricular mean pressures were determined by planimetric integration. The upper limits of the various pressures in normal subjects are as follows: right ventricular systolic pressure, 30 mm. Hg; right

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* Sanborn Poly-Viso Cardiette.

ventricular end-diastolic pressure, 5 mm. Hg; and mean right auricular pressure, 5 mm. Hg.[1] Four patients with chronic constrictive pericarditis were studied. Pericardiectomy was performed on two patients and postoperative pressure curves were obtained in one of these.

Results

Case Report

Case 1. C. T. This 20 year old man was admitted to the hospital in January, 1948 complaining of aching in the anterior chest, swelling of the abdomen, and ankle edema of four months duration. He had suffered a crush injury of the chest 10 months previously. The jugular veins were slightly distended. The heart was normal in rhythm and no murmurs were audible. The blood pressure was 100/72. The liver edge was palpable 4 cm. below

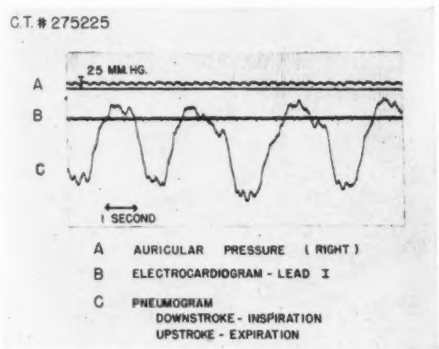

Fig. 1. Right auricular pressure tracing in case C. T. (Description in text.)

the costal margin and there were signs of free fluid in the peritoneal cavity. Fluoroscopy of the chest showed slight enlargement of both left and right ventricles. The pulsations of the heart were diminished. Venous pressure was 330 mm. of saline. Electrocardiogram showed sinus tachycardia with low voltage and inverted T waves in leads I, II, III, and CF_4. Circulation time from arm to lung (ether) was 40 seconds and from arm to mouth (Macasol) was 46 seconds.

The right auricular pressure curve obtained by cardiac catheterization showed an M or W shaped pattern with a mean value of 16 mm. Hg without respiratory variation (fig. 1). Unfortunately, the tip of the catheter could not be introduced into the right ventricle.

A clinical diagnosis of constrictive pericarditis was made and the patient was operated on in June, 1948. The pericardium was pale, thickened and fibrous, and visible pulsations were minimal. The pericardium and epicardium were removed from the anterior surface of both ventricles, laterally to the phrenic nerve and medially well around the right ventricle. The apex was completely freed. As the thickened cardiac envelope was relieved the heart action became more forceful. Since the operation the patient has improved and has returned to a full work program. The venous pressure fell to 130 mm. of saline. In March, 1952 he was well and cardiac catheterization was attempted twice unsuccessfully.

Case 2. M. F. This 61 year old woman was first seen in the Medical Out-Patient clinic in December, 1948 with complaints of exertional dyspnea and swelling of the legs and abdomen. She had had a history of rheumatic fever in childhood. The pertinent findings were: elevated venous pressure, moist rales over both lung bases, apical systolic and diastolic murmurs, enlarged liver and spleen, and ascites and edema. The working diagnosis was rheumatic heart disease with mitral stenosis and insufficiency associated with congestive heart failure. During the following three years she was treated with bed rest, digitalis preparations, mercurial diuretics, low-salt diet, and, most recently, ion exchange resins. In spite of this regimen her edema was still marked. In November, 1951 the patient was restudied. Physical examination revealed distended jugular veins, massive edema of the legs, and cardiac enlargement both to the left and right. She had auricular fibrillation without a pulse deficit. There was a loud systolic murmur over the precordium, loudest at the apex. A diastolic click was suspected by two observers. The pulmonic second sound was accentuated. Moist rales were present at both lung bases, and there was moderate ascites. Roentgenograms and fluoroscopy of the chest showed enlargement of the right auricle but not of the left, and extensive calcification of the pericardium. Cardiac catheterization revealed a right ventricular pressure pattern characteristic of constrictive pericarditis with a rapid diastolic dip followed by a high diastolic plateau (fig 2.). The systolic and end-diastolic pressures were 52 and 18 mm. Hg respectively. The right auricular pressure showed two upward and two downward deflections with a mean pressure of 21 mm. Hg. The downward deflections did not touch the baseline and the second downward deflection coincided with the ventricular diastolic dip. An interauricular septal defect was also demonstrated.

Case 3. H. A. This 54 year old man was admitted in August, 1951 with symptoms of malaise, fatigue, anorexia, weight loss, exertional dyspena and cough for more than two weeks. He had always enjoyed good health until the present illness. The patient was febrile and toxic with distended jugular and thoracic veins. Expiratory rales were heard at both lung bases posteriorly. The heart sounds were distant and there was an apical systolic murmur as well as

a precordial friction rub. The blood pressure was 92/70. The liver was 3 cm. below the costal margin by percussion. Roentgenograms and fluoroscopy of the chest revealed an enlarged cardiac shadow with diminished heart pulsations. Electrocardiograms showed auricular fibrillation on admission which spontaneously converted to sinus tachycardia on the following day. In addition, the voltage was low and the T waves in leads over the left precordium were flat. A tentative diagnosis of pericarditis, probably of tuberculosis etiology, was made. While in the hospital the patient developed bilateral hydrothorax requiring numerous thoracenteses on the right. The administration of Aureomycin, streptomycin and para-aminosalicylic acid failed to alter the course of his illness.

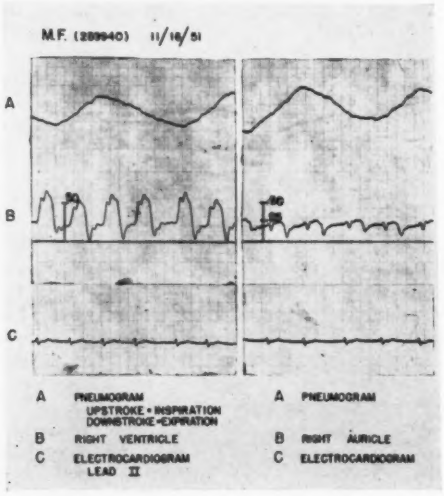

FIG. 2. Right ventricular pressure (left) and right auricular pressure (right) curves in case M. F. (Description in text.)

About two months after admission marked progression of his dyspnea was noted. The venous pressure was 170 mm. of saline. The area of cardiac dullness was not increased, but the heart sounds were more distant. Increasing pericardial effusion was suspected. A therapeutic pericardial tap yielded 100 cc. of straw-colored fluid. Cardiac catheterization prior to the pericardial tap showed a ventricular pressure pattern characteristic of constrictive pericarditis (fig. 3). This did not change significantly after removal of the pericardial fluid. The ventricular systolic and end-diastolic pressures were 35 and 15 mm. Hg respectively. The right auricular pressure pattern was not wholly characteristic, but the downward deflection failed to reach the baseline and the mean pressure was elevated to 16 mm. Hg. Operation was not considered because of his poor condition. The venous pressure continued to increase and the patient died three months after admission. Postmortem examination revealed chronic constrictive pericarditis associated with acute tuberculous pericarditis and hydropericardium.

Case 4. R. W. This 58 year old man was admitted in October, 1951 with a history of weakness and fatigue for one year and ankle swelling for about five weeks prior to admission. In the past five years the patient had had periodic swelling of the ankles without chest pain, cough, dyspnea, or orthopnea.

There was pronounced edema of the legs and distended jugular veins. Examination of the lungs showed some dullness over the left base posteriorly, with diminished breath sounds. The heart was slightly enlarged to percussion. The lateral border was just outside the midclavicular line in the fifth

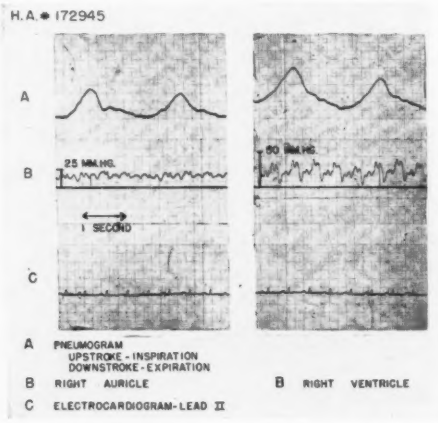

FIG. 3. Right auricular pressure (left) and right ventricular pressure (right) curves in case H. A. (Description in text.)

intercostal space. The rhythm was regular and the sounds were of good quality. No murmurs were heard. The abdomen was distended with signs of free fluid. The liver was palpable about 4 cm. below the costal margin.

An electrocardiogram showed low voltage and inverted T waves in the left precordial leads compatible with chronic pericarditis. Because of the presence of a QS wave in leads V_1–V_4 the possibility of an old anteroseptal infarct was suspected. Venous pressure was 320 mm. of saline. Fluoroscopy of the chest showed some enlargement of the cardiac shadow, the configuration of which did not change significantly with changing position. However, there was diminished amplitude of pulsation. A moderate amount of fluid blunted the left costophrenic angle.

The differential diagnosis between constrictive pericarditis and coronary artery disease with chronic

congestive failure was not clear cut in this case. Cardiac catheterization showed a right ventricle pressure pattern with a characteristic diastolic dip followed by a high diastolic plateau. The right ventricular systolic pressure was 36 mm. Hg and the end-diastolic pressure 21 mm. Hg. Because of the typical pressure patterns a diagnosis of constrictive pericarditis was made and the patient was prepared for pericardiectomy with mercurial diuretics and thoracentesis.

At the time of pericardiectomy there was marked thickening of the pericardium through which the pulsations of the heart were barely transmitted. This was particularly true over the region of the left ventricle. The pericardium was incised and about 300 cc. of fluid under pressure was obtained after which the excursion of the ventricle improved. The pericardium over the right ventricle was then incised and no free fluid was found. The pericardium was dissected free from the right side of the heart up to the auriculoventricular septum and towards the right side until both the inferior and superior venae cavae could adequately be visualized. There was no evidence of constriction around the venae cavae. Decortication around the left ventricle was more difficult. In some areas there was marked calcification and much of the thickened epicardium had to be removed by sharp dissection. The left ventricle was decorticated laterally to the phrenic nerve and superiorly to the auricle. The apex was freed from the diaphragm. The pulsation of the heart then increased markedly and the apparent increased filling was indicated by the bulging of the heart during the diastole. Pathologic examination of the pericardium showed fibrosis and chronic inflammation. The day after operation the venous pressure had dropped to 130 mm. of saline and on the tenth postoperative day it was 100 mm. of saline.

Four months later the patient returned for follow-up studies. Physical examination revealed no abnormalities of the heart, lungs, or abdomen. A 12-lead electrocardiogram was not different from that taken preoperatively. A chest film showed a definite decrease in the size of the cardiac silhouette and the lung fields were clear.

Another cardiac catheterization was performed and the pressure tracings from the right heart showed distinct changes in comparison with the curves obtained before operation (fig. 4). In the right ventricle there was no longer a distinct diastolic dip followed by a high diastolic plateau. Instead, the pressure at the end of systole reached the baseline and gradually rose during diastole to a level of about 8 mm. Hg. The right ventricular systolic pressure was 39 mm. Hg. The right auricular pressure curve still retained the M shaped pattern but the mean pressure was reduced to 5 mm. Hg. In addition, the downward deflections touched the baseline and definite respiratory variations were observed,

The ratio between the right ventricular end-diastolic and systolic pressures in patients with constrictive pericarditis has not been previously described. The right ventricular systolic pressure may markedly increase in certain cardiopulmonary diseases, such as pulmonary stenosis, severe mitral stenosis, and chronic pulmonary diseases. However, the right ventricular end-diastolic pressure usually remains within normal limits unless right ventricular failure is also present. In the latter condition, both right ventricular

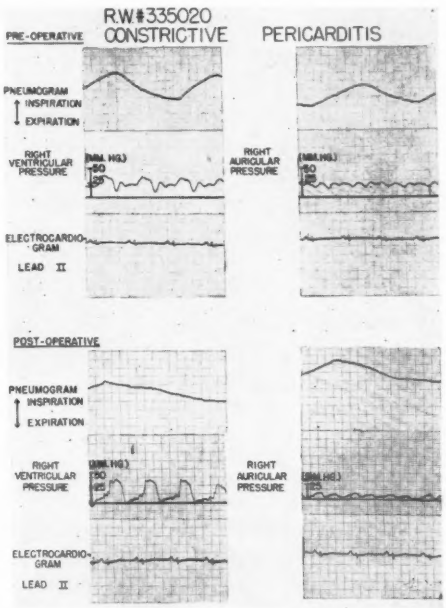

FIG. 4. Preoperative and postoperative right ventricular and right auricular pressure tracings in case R. W. (Description in text.)

systolic and end-diastolic pressures may be abnormally high, but in our experience the ratio between the end-diastolic and systolic pressures is always less than one-third.

The significance of this ratio in constrictive pericarditis is shown in figure 5. The end-diastolic to systolic pressure ratio was always less than one-third in 132 patients with various cardiopulmonary diseases other than constrictive pericarditis studied in this laboratory. However, the ratio was more than one third in 15 patients with constrictive pericarditis

where measurements of the pressure were made or could be obtained (including 12 patients reported by other investigators). In six patients following pericardiectomy (including five patients reported in the literature and one of our own cases) the ratio is below one-third with the exception of one patient in whom the cardiac catheterization was performed only 12 days after pericardiectomy.

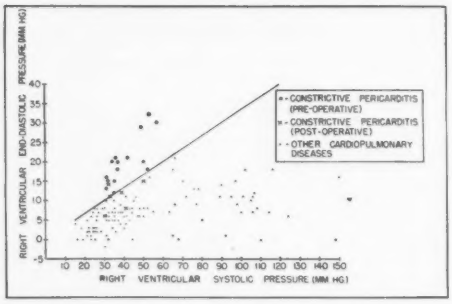

FIG. 5. This graph shows the ratio between right ventricular systolic and end-diastolic pressures in 132 patients with various cardiopulmonary diseases other than constrictive pericarditis, in 15 patients with constrictive pericarditis, and in six patients with constrictive pericarditis following pericardiectomy.

DISCUSSION

The preoperative pressure patterns of the right auricle and ventricle presented in this report agree with those described by other investigators.[1-3] Hansen and associates[2] noted disappearance of the characteristic pattern of the pressure curve in patients following successful pericardiectomy. Similar change was also observed in one of our cases (case 4).

We believe that the recording of the right auricular and ventricular pressure curves may be a very useful diagnostic aid in constrictive pericarditis. We agree with Hansen and coworkers[2] and McKusick[3] that the pressure patterns are characteristic of this condition. However, the right ventricular pressure pattern is not pathognomonic for constrictive pericarditis since similar patterns have been observed in patients with right ventricular failure and myocardial fibrosis.[2, 3]

The mechanism of the characteristic right auricular and ventricular pressure patterns in constrictive pericarditis has been discussed by Hansen and associates and McKusick.[2, 3] These are caused mainly by impaired diastolic filling of the right ventricle. The right ventricle is almost completely empty immediately following the systolic ejection. The resulting drop in pressure constitutes the "diastolic dip" which is actually more apparent than real. In the absence of a diastolic plateau, this "dip" is a normal phenomenon, and touches or falls below the baseline. Both limitation of ventricular distension by the constricted pericardium and the high right auricular pressure cause the right ventricle to fill to its maximum capacity. Therefore, the "diastolic dip" usually does not touch the baseline but suddenly rises to a high diastolic plateau until it reaches the end-diastolic pressure.

The end-diastolic pressure in the right ventricle is exceedingly high, so that the mean tight auricular pressure has to be high in order ro maintain a positive gradient between these two chambers. As the right ventricle fills up rapidly the drop in the auricular pressure is relatively insignificant and of short duration. This explains why the upward deflections of the right auricular pressure are high and the downward deflections fail to reach the baseline. The second downward deflection of the right auricular pressure almost coincides with the ventricular diastolic dip in time, shape, and amplitude. Therefore, the change of the pressure pattern in the right ventricle is primary, and that in the right auricle is secondary.

The ratio between the right ventricle end-diastolic and systolic pressures may be useful in differentiating constrictive pericarditis from other conditions which give similar right auricular and ventricular pressure patterns. It is our experience that this ratio is not above one third in conditions other than constrictive pericarditis. Elevation of the end-diastolic pressure is associated with a corresponding rise of the systolic pressure in other cardiopulmonary diseases. On the other hand the right ventricular systolic pressure is only slightly increased in a typical case of constrictive pericarditis and the end-diastolic pressure is markedly elevated; furthermore, the ratio

between the end-diastolic and systolic pressures is always more than one third.

Striking changes occur in the right ventricular and auricular pressure patterns of patients with constrictive pericarditis after successful pericardiectomy. The "diastolic dip" in the right ventricular pressure curve becomes less prominent, largely due to more adequate filling of the right ventricle. The diastolic plateau almost disappears and the end-diastolic pressure is much lower. The right auricular pressure curve may retain an M shaped pattern but the mean pressure returns to normal value. The downward deflections touch the baseline and respiratory variation appears in the pressure curves. It is reasonable to assume that if the pericardiectomy is not satisfactory, the preoperative pressure pattern may be retained. Therefore, the changes in the right auricular and ventricular pressure patterns may be useful in evaluating the results of pericardiectomy.

Summary

1. The right auricular and ventricular pressure patterns in four patients with constrictive pericarditis are described.

2. The right auricular pressure is markedly elevated and shows an M or W shaped pattern with two upward and two downward deflections. The downward deflections do not touch the baseline and the pressure curve shows no respiratory variation.

3. The right ventricular pressure curve consists of (*a*) a slightly elevated systolic pressure, (*b*) a rapid "diastolic dip" followed by a high diastolic plateau and end-diastolic pressure and (*c*) an end-diastolic to systolic pressure ratio of more than one-third. The significance of this ratio is emphasized. This ratio may help to distinguish constrictive pericarditis from simulating conditions where a high end-diastolic pressure may be recorded.

4. The pressure patterns of one patient show distinct changes following successful pericardiectomy.

5. The mechanism of the production of the pressure patterns is discussed.

Acknowledgments

The authors wish to express their thanks and appreciation for the secretarial aid of Mrs. Julia Gooding and the technical assistance of Miss Carol Gouverneur and Mr. S. John Vernarelli.

Sumario Español

Las presiones intracardíacas de cuatro pacientes con pericarditis constrictiva son descritas. El significado de la proporción alta entre la presión intraventricular derecha al final de diástole y la presión sistólica es demostrado. Cambios postoperatorios se describen en un paciente y el mecanismo de la producción de estas presiones se discute.

REFERENCES

[1] Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S., and Richards, D. W., Jr.: Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardio-circulatory disease. J. Clin. Investigation **25:** 639, 1946.

[2] Hansen, A. T., Eskildsen, P., and Gotzsche, H.: Pressure curves from the right auricle and the right ventricle in chronic constrictive pericarditis. Circulation **3:** 881, 1951.

[3] McKusick, V. A.: Chronic constrictive pericarditis. 1. Some clinical and laboratory observations. Bull. Johns Hopkins Hosp. **90:** 3, 1952.

[4] Wood, E. H., Geraci, J. E., Pollack, A. A., Groom, D., Taylor, B. E., Pender, J. W., and Pugh, D. G.: General and special technics in cardiac catheterization. Proc. Staff. Meet. Mayo Clin. **23:** 494, 1948.

Parietal Focal Block: An Experimental and Electrocardiographic Study

By V. Alzamora-Castro, M.D., Ricardo Abugattas, M.D., Carlos Rubio, M.D., José Bouroncle, M.D., Cesar Zapata, M.D., Eduardo Santa-María, M.D., Guido Battilana, M.D., Teodoro Binder, M.D., Ricardo Subiría, M.D., and David Paredes, B.S.

A method of producing focal ventricular block is described. The sequence of the electrocardiographic variations is ascribed to changes in the velocity and direction of the excitatory process in the ventricular wall. The epicardial electrocardiograms resemble those considered indicative of ventricular hypertrophy or of "incomplete" or of "complete" bundle branch block. When the focal block is pronounced a positive deflection appears in the cavitary tracing. The ventricular blocks can be subdivided into "conduction blocks" and "fiber blocks," the former produced by the delay of the stimulus in the specialized conduction system and the latter produced by the delay of the excitatory process in the ordinary heart muscle.

IN the past, focal blocks have proved difficult to produce experimentally. Recently, however, Frau obtained satisfactory results by the infiltration of quinine salts into the ventricular walls.[1] We have found that certain substances when injected into a coronary artery produce a parietal focal block. We believe that the results of these experiments have theoretic and practical importance. Preliminary observations have been already published.[2]

Method

In 46 dogs 92 experiments were performed. Observations were made after splitting the sternum and opening the pericardial sac. Fresh saline solutions of 2.5 or 5 per cent cocaine chlorhydrate were used, and small amounts varying from 0.1 to 0.5 cc. were injected into the coronary arteries. In several experiments saturated solutions of morphine, 1 per cent solutions of strychnine and other substances were also injected. The results were similar to those produced by cocaine. In most instances the anterior descending coronary artery was used, but in several experiments injections were given into the smaller vessels seen upon the epicardial surface of the right or left ventricles. In two instances the injections were given before and after cutting the left branch of the bundle of His.

The right arm terminal of the electrocardiograph was connected to the right hind leg through a nonpolarizable electrode, and the left arm terminal was connected to the exploring electrode through a similar nonpolarizable boot.[2] A rather large, olive shaped, electrode of German silver was introduced in the ventricular cavities, the indifferent electrode was attached to the left hind leg. Direct leads were taken upon the epicardial surface of the ventricular muscle supplied by the artery in which the injection was given. Control electrocardiograms were always taken; during the experiments tracings were obtained from distant ventricular zones, and occasionally curves were recorded while the exploring electrode was moved slowly over the epicardial surface. Cavitary leads were obtained where the more illustrative electrocardiographic changes were observed; curves were also taken while the electrode was moved in the ventricular cavity. Direct-writing electrocardiographs were found to be useful in locating the most convenient points for obtaining permanent records.

Results

The saline solution of cocaine when injected in a coronary artery caused a "parietal focal block" (p.f.b.) in the ventricular territory irrigated by the vessel. The focal block developed rapidly while the injection was being given, and disappeared gradually in 15 to 30 minutes. The electrocardiograms taken while the exploring electrode was moved slowly over the epicardial surface demonstrated that the ventricular region where the parietal focal block was maximal was encircled by zones in which the degree of the block gradually decreased (fig. 1). The blocked ventricular zone was found

From the Heart Laboratory, Hospital Dos de Mayo, University of San Marcos Medical School, Lima, Peru. This study was supported in part by the W. K. Kellogg Foundation, Battle Creek, Mich.

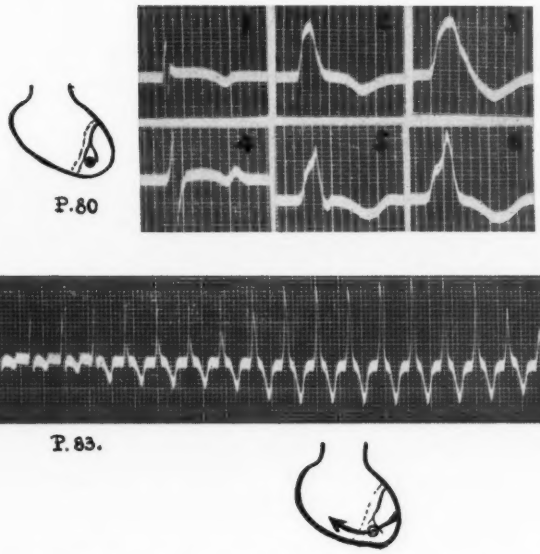

FIG. 1. *Left parietal focal block and left bundle branch block.* Electrocardiogram 1 was taken upon the epicardial surface of the left ventricle before the experiment. Tracings 2 and 3 were recorded at the same point while parietal focal block was progressing. When focal block disappeared the left branch of the bundle of His was cut. Electrocardiogram 4 was taken at the same epicardial point when left bundle branch block was present. Tracings 5 and 6 were obtained when left bundle branch block and parietal focal block coexisted. The artery which was injected and the site of the exploring electrode are indicated in the diagram.

The electrocardiographic changes in parietal focal block. The lower tracing was taken while the exploring electrode was moved slowly over the epicardial surface following the direction indicated by the arrow. The electrocardiographic changes clearly demonstrated that the blocked region is encircled by ventricular muscle in which activation is normal and that the average degree of block is more pronounced in the central zone than in the periphery.

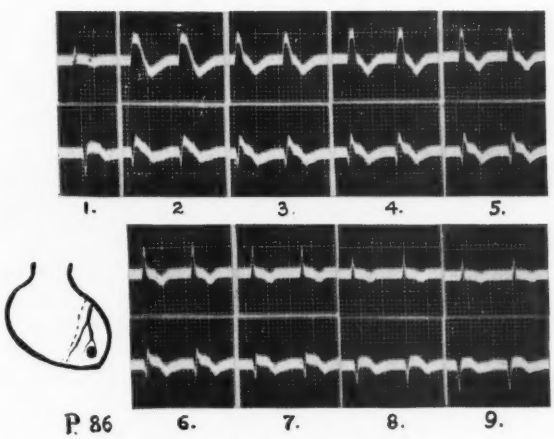

FIG. 2. *Left parietal focal block.* In this figure the control curves and those showing the sequence of the electrocardiographic manifestations in the epicardial and endocardial leads are seen. The curves were taken at short intervals during the experiments while the electrodes remained immobile.

to be surrounded by muscle in which the excitatory process was normal.

Disturbances of the heart rhythm and changes in the heart rate were rarely observed. In the ventricular wall where the block occurred the contractile activity locally decreased and this phenomenon had some relation to the degree of block.

The electrocardiographic changes in the epicardial leads. In right or left parietal focal block the terminal S waves when present in the control tracings disappeared rapidly when the block progressed (figs. 3 and 4). In left focal block the Q waves, when recorded in the control curve, persisted or became more prominent when the block progressed. Occasionally Q waves were only observed when the block was pronounced. In right parietal focal block the R deflection of septal origin remained almost unchanged while striking variations were seen in the deflections representing the electrical activity of the free wall of the right ventricle (fig. 4). In some cases when the ventricular excitation was normal, the R waves of unipolar direct leads taken upon the epicardial surface of the right ventricle represented the combined electrical effects produced by activation of the septum and those produced by the activation of the underlying ventricular wall (fig. 3). In figure 3, as the block progressed the size of the R and S waves diminished, the R-S ratio was altered but no definite changes were observed in the RS duration. When the block progressed even more the RS duration was prolonged and a notch heralding the late positive deflection was seen in the ascending limb of the S wave. In all cases in pronounced right parietal focal block the ventricular complexes were of the rsR′ type (figs. 3 and 4). In the unipolar direct epicardial leads in left and right parietal focal block tall and broad positive deflections were always recorded. As the block progressed the size of these deflections increased and their summits were inscribed gradually later (figs. 1, 2, 3, and 4).

The electrocardiographic changes in the cavitary leads. If the exploring electrode was placed far from the ventricular wall where the parietal focal block occurred the form of the electrocardiogram remained essentially the same. When the electrode was placed near to or in contact with the ventricular wall where the focal block occurred, conspicuous variations were observed. The cavitary potential became less negative while the block was incipient, and during developed block a late positive upstroke was recorded (figs. 2, 3 and 4). The size of the late positive deflection increased as the block increased. In right parietal focal block the endocardial electrocardiogram was of the rSr′ or rSR′ type (figs. 3 and 4). In left parietal focal block the cavitary tracings were of the Qr or QR type (fig. 2). When the exploring electrode in the ventricular cavity was moved away from the wall exhibiting focal block the size of the late upstroke diminished and finally

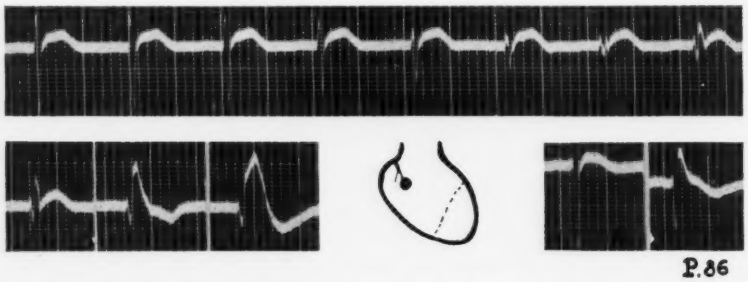

FIG. 3. *Right parietal focal block.* Electrocardiograms recorded while the parietal focal block progressed. When the block begins the size of the R and S waves diminishes, the RS relation changes but no definite variation in the RS duration is observed. A notch heralds the late R wave. When the block is pronounced the ventricular complex is of the rsR′ type. Cavitary leads taken before the experiment and when the block was pronounced can be seen at the lower right.

disappeared. In all experiments a late positive deflection in the cavitary tracing was recorded only when parietal focal block was already evident (figs. 2 and 4).

The electrocardiographic changes in left parietal focal block complicated by left bundle branch block. When these experiments were performed, soon after the injection notable electrocardiographic variations were observed (fig. 1). The form of the ventricular complexes was strikingly modified and the QRS interval was prolonged. The sequence of the electrocardiographic manifestations was similar to those recorded in uncomplicated cases of parietal focal block.

Discussion

Conduction blocks and fiber blocks. In the advanced stages of parietal focal block the tracings are no longer similar to those seen in experimental bundle branch block. This observation suggests that when parietal focal block is pronounced the course of the excitatory process is delayed in the muscle fiber itself. When one of the branches of the bundle of His is cut, no immediate changes can be expected in the intrinsic condition of the muscle fibers located in distant parts of the septum or in the ventricular walls. Experimentally produced bundle branch block is a good example of a "conduction block."[2] As may be seen in figure 1, when

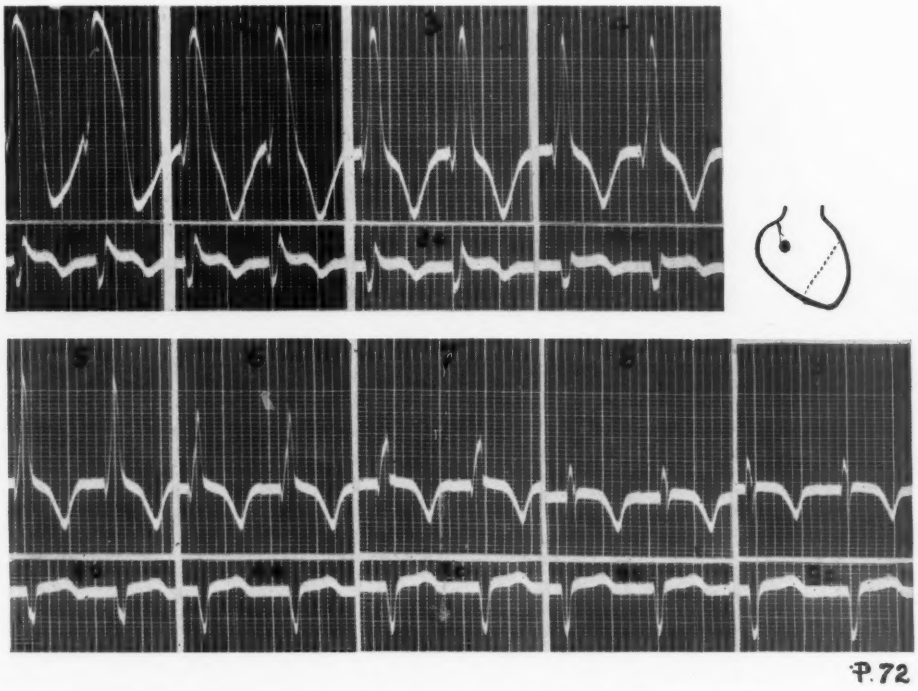

Fig. 4. *Right parietal focal block.* Epicardial and endocardial leads taken at intervals until the normal curve reappeared. In epicardial as well as endocardial leads small initial R waves are present. When parietal focal block is severe the negative downstroke following the initial positive deflection becomes prominent. Terminal S waves recorded when ventricular excitation is normal disappear soon after the block begins. Variations in the size of the late positive deflections are obvious. In cavitary leads positive late deflections are present only while parietal focal block is pronounced; when the block disappears the negativity of the cavitary potential gradually increases. Tracings resemble those which in man are considered representative of right ventricular hypertrophy, "incomplete" and "complete" right bundle branch block.

a left parietal focal block is produced after the section of the left branch of the bundle of His, notable variations in the shape and duration of the ventricular complexes are observed; these changes can be ascribed only to the slow and abnormal course of the excitatory process in the ordinary ventricular muscle. The foregoing observations demonstrated the existence of "fiber blocks." Since in the experiments herein discussed the blocking substance was injected into a coronary artery, it must be expected that in the ventricular territory irrigated by the vessel all of the muscle elements, even those located near the endocardium, were damaged; consequently the parietal focal block produced by this method probably represents a mixture of "conduction" and "fiber" block.[2] The subdivision of ventricular blocks into "conduction" and "fiber" block is consistent with the existing physiologic data. The Purkinje network delivers impulses more or less promptly to the contractile elements, but once the stimulus reaches the muscle fibers the spread and further course of the excitatory process must depend upon the actual condition of the ordinary cardiac fibers. In a future paper the electrocardiographic manifestations accompanying severe "fiber" block will be discussed.

The QRS changes in the epicardial leads. Under normal conditions in direct unipolar epicardial leads the S waves are not due to the electrical activity of the underlying explored zone, but to the electrical effects of some distant ventricular regions which are activated later.[3] In right or left parietal focal block the terminal S waves diminish in size or disappear rapidly when the block begins. In the blocked region excitation is still progressing when the activation is finished in the rest of the ventricular muscle; consequently, even when the focal block is incipient, there are no distant electrical forces that may produce negative potentials by the time the final part of the electrocardiogram is recorded.

The Q waves are due to the electrical activity of the ventricular regions that are activated earlier than the explored zone.[3] Since the spread of the excitation is delayed in the blocked region, in left parietal focal block the Q waves may persist, become more prominent, or are present only while the block is severe. In right parietal focal block the septum is not involved, therefore no changes can be expected in the initial positive deflection; similar observations have been made in human right ventricular blocks.[4] The S waves following the initial R deflections in right parietal focal block and the Q waves in left parietal focal block are produced by a similar process.

In the electrocardiograms obtained in the blocked region we may expect active balancing electrical forces only when activation is progressing in the rest of the ventricular muscle. Hence, while the initial part of the ventricular complex is influenced by distant electrical forces, the final part of the tracing represents the unbalanced potential variations of the explored zone. Under normal conditions a positive deflection is inscribed in a unipolar direct epicardial lead if the voltage developed across the wall beneath the exploring electrode increases more rapidly than the negativity of the adjacent ventricular cavity.[3] Once the ventricular muscle normally activated has passed into the resting electrical state, negative cavitary potentials no longer exist. Hence, in direct unipolar leads taken upon the epicardial surface of an island of ventricular muscle that is activated later, striking changes may be expected by the time the negativity of the adjacent ventricular cavity decreases or disappears. The size of the positive deflections in the epicardial leads in canine right or left parietal focal block may be partially due to the disappearance of the negative potential in the ventricular cavities. However, the presence of a positive deflection in the opposite endocardial leads clearly indicates that in determining the form and size of these deflections the abnormal course of the excitatory process in the ventricular wall also plays an important role.[2]

When the right parietal focal block begins (fig. 3), there is a delay in the activation of the ventricular wall beneath the electrode; hence the size of the R and S waves diminishes because the voltage developed across the explored ventricular wall is balancing the negative potentials of the ventricular cavity. The variations in the size and relation of the R and S waves that are important in the diagnosis of

right ventricular hypertrophy can, in this case, be ascribed to a minor degree of block. Striking changes may be observed in the form of the electrocardiograms while no definite prolongation of RS duration is noted. When right parietal focal block is more pronounced the explored ventricular wall becomes active even later, consequently the potential variations of the ventricular wall beneath the electrode are unbalanced and the late positive deflection rises above the base line. The foregoing analysis may explain the rSR′ type of ventricular complexes not only in canine parietal focal block but also in cases of human right ventricular block.[2]

The QRS changes in the cavitary electrocardiogram. The analysis of the electrocardiographic changes observed in man when ventricular blocks are progressing, suggests that in the involved ventricular walls the vector that represents the average direction of the excitation must be parallel or nearly parallel to the epicardial or endocardial surfaces.[5]

Under normal conditions, in human beings or in dogs, the outward spread of the excitation in the ventricular walls produces negative potentials in leads taken inside the ventricular cavities.[3] When the parietal focal block is incipient the negative potentials diminish. In parietal focal block the activation of the rest of the heart muscle remains unchanged, consequently, variations in the magnitude of the cavitary potentials solely can be ascribed to changes in the electrical activity of the ventricular wall where the block is progressing. In minor degrees of block the ventricular wall contributes less effectively or not at all to the production of either positive or negative potentials in the ventricular cavities. When the parietal focal block is severe a late positive deflection is recorded in the cavitary lead, and the size of this deflection increases as the block increases. A similar positive deflection is simultaneously inscribed in the opposite epicardial lead. Positive potentials in two leads taken upon the opposite surfaces of the same ventricular wall suggest that the average direction of the electrical forces developed in the ventricular wall is parallel, or nearly so, to the epicardial or endocardial surfaces.[2] Probably the spread of the excitatory process in the ventricular wall where a severe block occurs can be compared to the course of the excitation in the normal auricular muscle.[2] The experiments of Pruitt, Essex and Burchell in isolated strips of heart muscle support this point.[6] It was evident in all experiments that the positive upstroke in the cavitary lead appeared only when the block was severe. The presence of a positive potential in the ventricular cavities can be considered a reliable index of the degree of block. It is important to mention that Sodi-Pallares, Estandia, Soberon and Rodriguez, using cavitary leads, found a positive potential only when the human left ventricular block was definitely established.[7] The electrocardiograms become normal when the velocity of the excitation wave increases and when the excitatory process spreads radially from the endocardium towards the epicardium.[2]

The changes in the T waves. In normal conditions the direction and contour of the T waves depend at least partially upon the relative duration of systole in the endocardial and in the epicardial layers.[8] In parietal focal block the size and contour of the positive deflections representing depolarization can be correlated to the size and contour of the negative waves representing recovery. Considering the abnormal and slow course of the excitatory process in parietal focal block, it may be suspected that the muscular units that are activated first are first in recovering, and the muscle fibers that are activated later are also later in passing to resting electrical state.

Conclusions

The form and duration of the epicardial and endocardial electrocardiograms in the different types of ventricular block depend mainly upon the velocity and direction of the excitatory process in the ventricular walls. The tracings obtained when right or left parietal focal block is incipient are similar to those that can be considered representative of right or left ventricular hypertrophy. The electrocardiograms recorded when parietal focal block is pronounced resemble those of "incomplete" or "complete" bundle branch block. In direct or semidirect unipolar leads, when the ventricular

excitation is normal, the voltage developed across the ventricular wall and other characteristics may indicate the thickness of the explored heart muscle. It is also evident that under normal conditions the differences existing between the precordial leads exploring the right and left ventricles can be ascribed mainly to the different thicknesses of the underlying ventricular walls. Under pathologic conditions it is not known if the tracings considered indicative of right or left ventricular hypertrophy actually represent "conduction block," "fiber block" or both.[2] However, notorious variations in the form of the electrocardiograms may be expected only if a ventricular block exists.

It follows that probably the designation bundle branch block is often but not always correctly applied. The experiments demonstrated that the tracings obtained in focal blocks can be mistaken for those observed in bundle branch blocks. It is probable that in human pathologic states "conduction block" can often be complicated by "fiber block." It may be presumed that "fiber block" has more definite clinical significance than "conduction block." Pure "conduction block" is compatible with a normal ventricular muscle, while "fiber block" indicates disturbances of the contractile muscle elements.

Summary

In ventricular blocks the form and the duration of the electrocardiograms can be ascribed mainly to changes in the velocity and direction of the excitatory process in the ventricular walls. Any delay in the passage of the impulse through the branches of the bundle of His, its subdivisions or the Purkinje network is defined as "conduction block." The delay of the excitatory process in the ordinary heart muscle is defined as "fiber block." "Mixed block" of these two categories also exists.

In cases of canine experimental focal block the form and other characteristics of the electrocardiograms resemble those tracings that in humans may be considered representative of right or left ventricular hypertrophy, or of "incomplete" or "complete" right or left bundle branch blocks.

In parietal focal block positive and broad deflections are recorded in leads taken on the epicardial and endocardial surfaces. In leads taken at opposite points separated only by the thickness of the ventricular wall, positive and broad deflections clearly indicate the average direction and velocity of the excitatory process in the ventricular wall where the block occurs.

The analysis of the QRS-T changes in experimental focal block helps explain the form of the epicardial and endocardial electrocardiograms in the different types of human ventricular blocks.

Sumario Español

Un método de producir bloque focal ventricular se describe. La sequencia de variaciones electrocardiográficas es ascrita a los cambios en la velocidad y dirección del proceso excitatorio en la pared ventricular. Los electrocardiogramas epicardiales se asemejan a aquellos considerados indicativos de hipertrofia ventricular o de bloque completo o incompleto del paquete de His. Cuando el bloque focal es pronunciado una deflección positiva aparece en el trazado cavitario. Los bloques ventriculares pueden ser subdivididos en bloques de conducción y en bloques de fibra, el primero producido por el retardamiento del impulso en el circuíto de conducción especializado y el segundo producido por el retardamiento del proceso excitatorio en el músculo del miocardio.

REFERENCES

[1] Frau, G.: La pathogenie des troubles de la conduction ventriculaire. Cardiologia **19:** 2, 1951.

[2] Alzamora-Castro, V., Abugattas, R., Rubio, C., Battilana, G., Zapata, C., Bouroncle, J., Santa-Maria, E., Subiria, R., Binder, T., and Paredes, D.: El bloqueo intraventricular derecho focal canino. El bloqueo intraventricular derecho humano. Estudio electrocardiográfico comparativo. Rev. Peruana cardiol. **1:** 1, 1952.

[3] Wilson, F. N., Rosenbaum, F. F., and Johnston, F. D.: Interpretation of the Ventricular Complex of the Electrocardiogram. In: Advances in Internal Medicine. New York, Interscience Publishers, 1947. Vol. 2.

[4] Alzamora-Castro, V., Battilana, G., Abugattas, R., Rubio, C., Bouroncle, J., and Zapata,

C.: El curso de la excitación ventricular en el corazón humano cuando la activación es normal y cuando hay bloqueo de conducción derecho. Rev. argent. de cardiol. **18:** 1, 1951.

[5] —, —, —, —, —, —, AND SANTA-MARIA, E.: Los bloqueos intraventriculares. An. Fac. med., Lima **34:** 313, 1951.

[6] PRUITT, R. D., ESSEX, H. E., AND BURCHELL, H. B.: Studies on the spread of excitation through the ventricular myocardium. Circulation **3:** 418, 1951.

[7] SODI-PALLARES, D., ESTANDIA, A., SOBERON, J., AND RODRIGUEZ, M. I.: The left intraventricular potential of the human heart. Am. Heart J. **40:** 655, 1950.

[8] WILSON, F. N., MACLEOD, A. G. AND BARKER, P. S.: The T-deflection of the electrocardiogram. Tr. A. Am. Physicians **46:** 29, 1931.

CLINICAL CONFERENCES

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Management of Moderately Severe Arterial Hypertension

By IRVINE H. PAGE, M.D.

I SHALL review with you the course of a patient with the aim of demonstrating our approach to the treatment of severe essential hypertension. We are a long way from knowing all the answers; indeed we must admit that many of the basic mechanisms which sustain and regulate normal arterial pressure are obscure; still, interest in and knowledge of the arterial hypertensions has grown astonishingly in the past 15 years.

Dr. Piette, would you present an abstract of the patient's history?

DR. PIETTE: This 52 year old man has been in good health most of his life. His mother died at 64 years of heart failure and his father at 69 of a stroke. When he was 22, a college health examiner told him his blood pressure was slightly elevated on one occasion, but not sufficiently to cause any concern. He passed several life insurance examinations; on two of these occasions he was asked to return for recheck of blood pressure. The last time was 15 years ago. His blood pressure was found to be definitely elevated six years ago during a routine company physical examination. He had no symptoms and he gave it no thought. About three years ago he experienced occasional morning headaches; two years ago these became regularly recurrent. Some nine months ago he noted shortness of breath on slight exertion and, more recently, that he slept best when supported by two or three pillows. About three months ago, his ankles became swollen during hot weather. He has had nosebleeds on two or three occasions and twice in the past three months episodes of transient weakness of the right arm and difficulty in forming words.

He is an active, successful businessman. He seems socially and domestically well adjusted. He gives the impression of having a proper self-confidence and ability to express his feelings. He is not unduly depressed or concerned by what has happened, but is intent on a definitive resolution of his problem.

DR. PAGE: You will notice that this man's story is almost monotonously familiar. In fact, that is the reason it is brought up for discussion. I realize it would be more dramatic to present some unusual situation, some rarity, such as pheochromocytoma, because of our more satisfactory understanding of its nature and treatment. But that is not our main problem. It is the commonplace and the familiar which is also the obscure; this we must constantly try to illumine.

The first point to be established is whether or not we can identify a single cause of this man's hypertensive disease. Glomerulonephritis, pyelonephritis, pheochromocytoma, coarctation of the aorta and many rarer causes should be considered (in women, of course, toxemia of pregnancy should also be considered). These are classified and tabulated for ready reference on page 25 of that excellent text, *Hypertension: Its Diagnosis and Treatment* (second edition).

DR. TAYLOR: The most commonly overlooked of these is pyelonephritis. This simply should not be; prompt and proper treatment with antibiotics and antibacterials should eliminate this as a cause of hypertensive disease. I have become almost a missionary for this point of view; still, hardly a week passes without my seeing one or more victims of this sort of neglect.

From the Research Division of the Cleveland Clinic Foundation, and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

A PHYSICIAN: Dr. Taylor, do you perform excretory urography regularly in order to exclude unilateral renal disease and polycystic kidneys?

DR. TAYLOR: We routinely perform excretory urography not so much for the detection of rare pheochromocytomas—which urograms rarely define—and unilateral renal disease, but as an indication of renal tubular function.

Now, in this man's case, this question does not seem to arise. Rather, the urgent problem is to relieve the damage his hypertension has caused before spending his time and ours in looking for causes we may never find, or in trying this or that obscure means of lowering his pressure. I take it that he is already on a low-salt diet, has been digitalized and is being weighed daily.

DR. CORCORAN: This man's disease was until recently asymptomatic. He comes now for the relief of symptoms caused by hypertensive vascular disease; this disease results in large measure from persistent elevation of arterial pressure. Consequently, the lowering of pressure to a reasonable level is a paramount issue; any other treatment is a stop-gap merely.

DR. PAGE: You both think, then, that there is still some future for those who want to specialize in cardiovascular disease? There is always geriatrics, just in case, and the more hypertension you cure, the more geriatrics there will be.

The heredity in this patient favors the diagnosis of essential hypertension, and it is rather strongly weighted against him. But notice that both parents lived fairly long lives, despite manifest vascular disease. I think it makes a difference and it is always a relief to hear that the family is relatively long lived in spite of the occurrence of vascular disease in both parents.

I won't dwell on the many interesting problems associated with the social and economic aspects of hypertension. Suffice it to say at the moment that at long last some statisticians and insurance companies have had the good grace to allow people to die of essential and malignant hypertension rather than piecemeal from uremia, apoplexy, "nephritis" or heart failure. I feel sure that this failure to recognize the nature of the disease is one of the many reasons why hypertension has been such a difficult disease "to sell" to physicians and the laity.

A PHYSICIAN: Dr. Page, you use the words "essential hypertension and malignant hypertension" as if they were separate diseases. Will you clarify this?

DR. PAGE: I suppose "malignant hypertension" should rather be called the "malignant syndrome" because it appears under such a variety of circumstances. But the term malignant hypertension is so widely used, I doubt if anything we say is going to change it. Widespread necrotizing arteriolitis is the characteristic pathologic picture, and this is associated with marked diastolic hypertension. The syndrome usually is added to pre-existing hypertension of varied origin and usually of long duration. There are patients, though, in whom the arterial disease and the hypertension start almost simultaneously. To be more specific, the malignant syndrome is probably not a separate disease but something added to the existing hypertension.

The fact that slight transient hypertension was discovered when this patient was 22 brings up an interesting and often delicate problem. When slight transient hypertension is found, should the diagnosis of essential hypertension be made? What do you think, Dr. Corcoran?

DR. CORCORAN: I certainly do not think an unequivocal diagnosis should be made. There is seldom any hurry about making a final diagnosis in this disease. You may recall that when we were at the Rockefeller Institute Hospital we examined a number of lads from the Brooklyn Navy Yard because of transient hypertension. A good many years later some had developed severe hypertension, but many of them were perfectly normal. It is from those with labile hypertension that the majority of the full-blown cases come, but it by no means follows that all persons with transient elevations of blood pressure will develop the disease. The family history should influence this decision.

DR. TAYLOR: The time of incipiency is

when the physician must be most alert in recognizing and treating whatever disease may be the cause of hypertension. There is no excuse for allowing anyone to go for years with recurrent "cystitis" until irremediable renal disease results in severe hypertension. "Principiis obsta; sero medicina paratur."

A PHYSICIAN: Dr. Page, do you always consider the possibility of coarctation of the aorta? How do you exclude it?

DR. PAGE: The diagnosis of coarctation of the aorta will rarely be missed if the femoral and pedal arteries are palpated at physical examination. Measurement of femoral blood pressure is desirable but this requires special cuffs for the sphygmomanometer. Even if the diagnosis were missed in the physical examination it should be picked up in the x-ray film by discovering notching of the ribs and absence or smallness of the aortic knob.

Before we get far afield in this discussion, we should consider whether this patient really has essential hypertension or not. The history is in its favor. Physical examination shows the arterioles in the eyegrounds to be sclerosed and constricted; there is arteriovenous compression and a few scattered hemorrhages are seen as well. But there is no papilledema; nor are there exudates, retinal edema or showers of hemorrhages, which are some of the findings which go to make the diagnosis of malignant hypertension. These fundus photographs will help you visualize the disturbance (fig. 1).

The episodes of transient weakness, aphasia, severe nuchal headache which the patient described, point to cerebrovascular disease. The shadow of the heart is enlarged on the x-ray film and the electrocardiogram shows both left ventricular preponderance and the strain pattern. Since the patient has already had bouts suggestive of cardiac failure, these observations fit in with what might be expected. Renal function was moderately reduced as shown by the reduced ability to concentrate urine. We use the Addis concentration test at the Clinic, which as you may know, has a lower limit of normal of 1.024 to 1.026. The best this patient could do was 1.018. The estimate of renal blood flow from the para-aminohippurate (PAH) plasma clearance showed 640 ml. per minute. There were demonstrated also cylindruria (100,000 casts), proteinuria, hematuria (2,100,000 red cells in 12 hour urine specimen). Dr. Corcoran always gives us new ideas about renal function, even after all these years.

DR. CORCORAN: That's harder to do every day. I have the impression that every tenth medical graduate is given a bottle of para-aminohippurate, a trained dog or patient, two catheters (one venous, one urethral) and a corner in the laboratory along with his diploma.

As concerns this man, he demonstrates what Dr. Taylor and I speak of as the cerebrorenal polarity of hypertensive disease; this is a high-flown way of saying that most people with advanced cerebrovascular disease have good kidneys, and that most with highly nephrosclerotic kidneys retain their brains.

Of course this man does have active nephrosclerosis, as is indicated by the sediment count; but the advantage to him of his relatively good renal function is that, in general, those who retain such function retain also the capacity to respond to appropriate hypotensive regimes in greater degree and for longer periods than those in whom advanced renal disease imposes what may be secondary and relatively irremediable hypertensive mechanisms.

A PHYSICIAN: From a practical standpoint, Dr. Page, could we get enough information about renal function from determination of the blood urea or the blood urea nitrogen?

DR. PAGE: I think not. Retention of urinary excretory products is a late manifestation of renal disease. It is the progress of the vascular disease in the kidneys that we wish to follow and this can only be done with the more discrete tests of kidney function.

The participation of adrenal cortical function in hypertension is still most controversial. The problem arises first from George Crile's concepts of adrenal function as expressed in his books on anoci-association and on man as an adaptative mechanism. Later some of us found that adrenal cortical function is essential to the maintenance of renal hypertension in dogs and Selye produced hypertension by giving desoxycorticosterone to uninephrectomized, salt-fed rats. Selye then developed the

concept that hypertension is a disease of adaptation, in which adrenal dysfunction is an essential mechanism. Still more recently, Green first and then others seem to have shown that bilateral adrenalectomy may be a means of arresting hypertensive disease and of lowering arterial pressure. But many are not convinced that adrenal mechanisms participate in the genesis of hypertension except in Cushing's syndrome and consider most of the work done

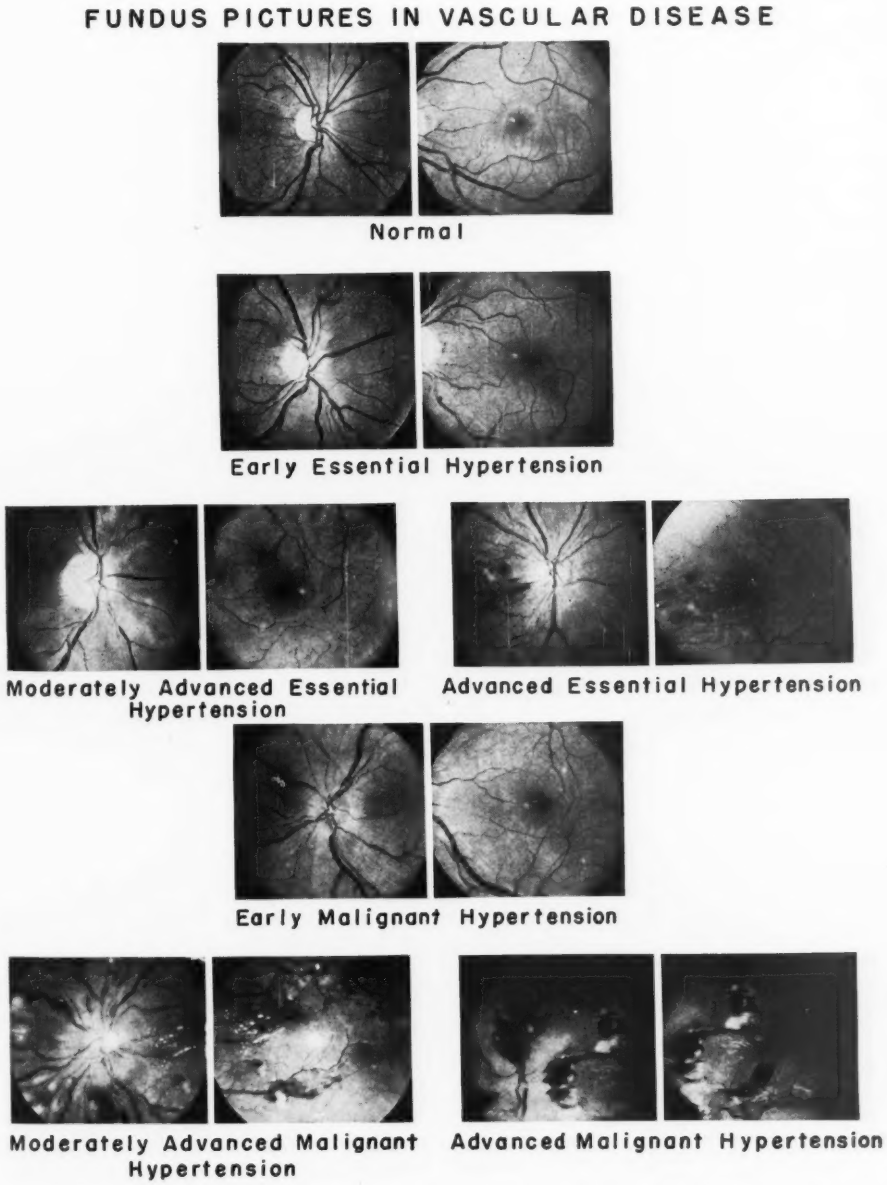

FIG. 1. Examples of the various stages of hypertension as reflected in the eyegrounds

in this field as an example of recondite pharmacology and most of the hypotheses as thinner than air. Dr. Harriet Dustan has done some work in this field and I would like to know her views on this healthy dichotomy of opinion.

DR. DUSTAN: I don't know the answer. I doubt that anyone knows enough to be as categorical as most are. What we have found is that some people with hypertension do show increased outputs of formaldehydogenic corticoid. That is the fact. The rest is opinion. We think this is due to an abnormality in the mode of corticoid excretion possibly consequent to renal damage and not a result of hypercorticoidism. Of course, desoxycorticosterone hypertension is a factor too, and so is the hypertension in Cushing's syndrome; the opposition to Selye's concept of "mineralocorticoid secretion" on the basis that no such corticosteroid could be demonstrated is having a hard time these past weeks with Simpson and Tais' demonstration of such a material in cortical extract and adrenal venous blood. The problem is still vexed by its methodology; obviously, a sufficient hypocorticoidism should remit hypertension in most instances, clinical or experimental; our scant clinical experience with adrenalectomy indicates this; but it also demonstrates that the operation is hardly worthwhile in the presence of advanced renal disease, and, in my view, hardly justifiable except as a last resort. Consequently, it will not have a place in the treatment of hypertension unless and until adrenogenic non-Cushing's hypertensions can somehow be segregated from the essential hypertensions.

DR. PAGE: I am going to assume, and I trust in this clinic with complete justification, that all the proper examinations have been made to rule out the ascertainable causes of hypertension, such as coarctation and pheochromocytoma. Never forget that the obvious is the easy thing to miss—and that must be obvious too.

A PHYSICIAN: Dr. Page, do you routinely do a screening test for pheochromocytoma? I understand such hypertension may masquerade almost precisely as essential hypertension. Inasmuch as it can be cured by operation in most instances, is it not wise always to do such a test?

DR. PAGE: Yes, indeed, we screen all patients for pheochromocytoma.

We can, therefore, make the diagnosis of severe essential hypertension in the patient who is being discussed, but what are we to do about it? Not more than 15 years ago there just wasn't much you could do about it. Today I am convinced that a lot can be done, but it takes a lot of doing by both patient and physician to accomplish a substantial benefit to the patient.

The first problem is to determine how rapidly the vascular disease is advancing; are we trying to put out a fire in the wastebasket or one in a dry forest in a high wind? Both started the same way—a cigarette—but the results differ appallingly.

A PHYSICIAN: Dr. Page, before you take up treatment, would someone explain the strain pattern and its significance in hypertension?

DR. PAGE: Dr. Taylor, you don't speak in public too harshly of the electrocardiogram, so will you answer the question?

DR. TAYLOR: The strain pattern, which consists of left axis deviation plus inversion of the T waves and depression of the S-T segments, is probably in fact due to strain since it occurs so characteristically in the presence of arterial hypertension, regardless of its mechanism. Further, it is the electrocardiographic change which is so often reverted toward or to normal when arterial pressure is reduced.

DR. PAGE: The simplest way to determine rate of progress is to select several reasonably objective criteria such as heart size, renal blood flow, examination of the eyegrounds, and to repeat the observation over periods of months, or at intervals determined by the rate at which vascular disease seems to be progressing. In a word, drastic disease justifies drastic treatment. Now having decided that this man has a fairly rapidly progressive severe essential hypertension, what are we to do for him? Obviously, the simpler measures such as rest and sedatives alone would be insufficient, although I believe more firmly than ever that some reorganization of the patient's life and a sound education in the nature of the disease is the beginning of

treatment of all chronic diseases. It is ignorance that breeds fear and fear augments the hypertension. Unfortunately, from my point of view, there are those who believe the less the patient knows the better.

A careful explanation of hypertension, and what the patient may expect, is in my experience never resented and usually deeply appreciated. I have felt strongly enough about it to write a small manual for the patient, not the physician, so that he may refresh his memory from time to time on the things most physicians would like him to know. To lose the benefit of this educational process is to lose one of the most reliable methods of lowering arterial pressure.

But education and the abolition of fear do not suffice. We must, therefore, consider diet, the ganglion blocking agents, hydrazinophthalazine (Apresoline), thiocyanate and nitroprusside, and finally sympathectomy. There is much talk regarding methods of selection of patients for each of these treatments. It is constantly stressed that patients should be selected "properly." Indeed, they should, but how? Despite the long list of suggested tests none of them have proved valuable in selection of patients for treatment. It is a great pity that this is so, because raising the successful outcome from an average of 20 to 30 per cent to 90 to 100 per cent would more than justify almost any of the current treatments.

Our patient is required by his work to do much traveling and for that reason only a very easily prepared, drastic low-salt diet would be of any use. The rice diet is the simplest and from the gastronomic point of view the one most awful to contemplate. Whether he is willing to live on such restricted fare only time will tell. I think it fair to say that few physicians are able to prescribe the diet with the confidence and enthusiasm of its originator, and much is lost in this failure. On the other hand, most of us do not believe in it that much either. If the patient lived at home, I am sure I would want him on a varied diet containing not more than 200 mg. of sodium as determined by the urinary excretion of sodium. This would be especially desirable if heart failure were impending, as it is in this patient. It would, then, seem best to request the company for which he works to transfer him from a travelling to an office job so that he could follow a diet which can be constructed with the aid of one of the new manuals, such as that issued by the American Heart Association, which allows enough variety to insure the patient's remaining on it for many months and perhaps years. The proper training in the use of diets is difficult: it is just as well that this is so, thus preventing automatically much

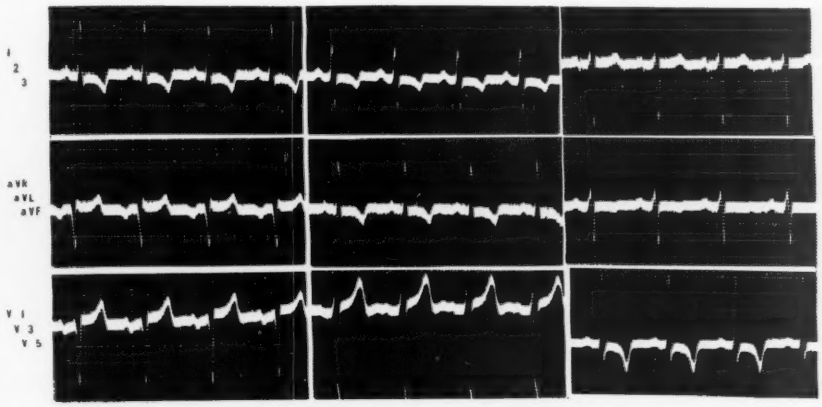

FIG. 2. The electrocardiogram shows left ventricular preponderance and the strain pattern RS-T depressed in leads I, aV_L and V_5. T inverted in I, II, aV_L and V_5

of the damage that careless dieting can engender. A change in a life long pattern is a big step in a patient's life. Remember that it might be your own.

A PHYSICIAN: I am a bit confused about low sodium diets. Some physicians seem to feel that restriction of sodium to 500 mg. a day is as useful as restriction of sodium in the diet to 200 mg. a day. The 500 mg. diet is of course a good deal easier for the patient.

DR. PAGE: While the 500 mg. sodium diet is much easier to prepare, our results show that the more rigid restriction is necessary if the most in blood pressure lowering is to be gotten out of the diet. With any low salt diet it must be recognized that the limits of error with many patients are great, so that a 500 mg. diet may mean anything from 300 to 1000 mg. Low-salt diets are in most cases an ordeal and if they are to be used, should be employed to achieve the greatest benefit. The patient, his wife, and the physician have to work at it! For those of you who feel the urge to prescribe low-salt diets lightly, I suggest you try the prescription yourself first.

A PHYSICIAN: Are the diets you speak of really practical?

DR. PAGE: Yes and no. Most of the "low-salt" diets aren't low-salt at all, hence they merely impose hardship and no advantages accrue from their use. The American Heart Association will shortly issue a low-salt cookbook which is practical and excellent. Thurman Rice has written a good one on the same subject. Salt-poor meats as well as bread, fish, and other foods are now on the market, so that things are becoming much simpler. Sodium-free condiments add much to the palatability of these diets.

The salt substitutes are always controversial. At the Clinic we offer them but find most patients prefer to do without them. Unfortunately, the best of the lot from the point of view of taste were those containing lithium chloride.

A PHYSICIAN: Would you mention some of the salt substitutes which may be used without getting into trouble such as that which occurred from the use of lithium chloride?

DR. PAGE: I believe Neocurtesal, Cosal and Diasal are the most popular. As you wisely point out, lithium caused us lots of trouble and it took us some time to find out why some of our patients on low salt diets were not doing well. It was an interesting experience but left me with a healthy respect for nature's way of doing business and for the need of penetrating studies before a drug or food substitute is sold.

DR. CORCORAN: Don't you think the urinary sodium should be measured at varying intervals? Not more than two or three out of 10 outpatients are able to keep their urine sodium constantly below the desired limit, and sometimes not from any fault of their own. Of course most patients at some time or another fool themselves as well as the doctor. Who could have thought a patient would get enough sodium from toothpaste or from chocolate bars to put her well above the 200 mg. sodium limit?

DR. DUSTAN: You haven't mentioned the dangers of these diets. There are some, you know! Extreme depletion of sodium, with weakness, nausea, vomiting and complete circulatory collapse, may occur, especially in hot weather, or after a large mercury-induced diuresis. The patient should be warned of it. It often takes longer to replace the sodium than one would think. A day or two may be required to restore depleted sodium to normal.

DR. PAGE: Unfortunately, time is moving on. The next problem I want to discuss briefly is the ganglion blocking agents such as tetraethylammonium chloride (TEAC) hexamethonium and Pendiomid. TEAC has been largely dropped in the treatment of hypertension because its action is much too transient. But it is still actively studied in the laboratory because of its unusual and fascinating properties.

Hexamethonium (Bistrium-Squibb) is a drug which has been introduced and quite extensively studied by English physiologists and clinicians, notably Ing and Barlow, along with Paton and Zaimis. Dr. Smirk of New Zealand, who not too long ago paid us such a delightful visit, has been most active in its study.

Hexamethonium blocks the transmission of impulses through both sympathetic and para-

sympathetic ganglia, but not completely. It is by no means a "total nervous blockade." Those impulses which adjust the caliber of vessels when the patient stands up are completely blocked. Thus, orthostatic hypotension is the most outstanding action of the drug. Since both sympathetic and parasympathetic ganglia are paralyzed, a variety of side effects result, such as stuffy nose, dry mouth, dilated pupils, inability to empty the bladder, and other symptoms. By far the most disturbing are the gastrointestinal upsets which more often than not follow both oral and parenteral injection. These may end in a disabling paralytic ileus unless promptly recognized.

DR. CORCORAN: I think it should be stressed at this point that both orthostatic hypotension and the gastrointestinal effects are dangerous. The patient must be very carefully instructed in order to avoid serious accidents.

DR. TAYLOR: This has not been sufficiently appreciated by most physicians. A barrage of premature newspaper and magazine publicity, aided and abetted by some physicians, has misled both public and physicians into believing that at last we have the answer and that it is a simple one.

DR. PAGE: I liked what one magazine called the drug—"Dangerous Hex." The premature and immoderate publicity given this drug has led many to believe that hexamethonium is a simply-administered, life-saving drug. In the first place, taken by mouth, its absorption is very irregular and the drug itself may cause even more irregularity. Not only may gastrointestinal complaints be very severe but, unless carefully controlled, the constitutional effects often become a threat to life. The usual initial dose is 125 mg. four times a day before meals. This is to be increased slowly until a total dosage of 3 to 4 Gm. per day is reached. We have seen so much difficulty from the oral use of hexamethonium that our enthusiasm for its use is small.

Some idea of how much the patient is receiving is gained by giving the drug parenterally. I think that a patient, intelligent and understanding wife is a prerequisite to successful use of parenteral hexamethonium. She must take blood pressure readings regularly and constantly adjust the dose according to need.

The development of tolerance is a very serious handicap. We have many patients in our clinic who become almost completely refractory to the drug after several months, with return of arterial pressure to the pretreatment levels. A few days without the drug usually restores responsiveness but the dosage must again be adjusted. There are many patients who simply do not respond to hexamethonium with a fall in average pressure. This is a point which seems to be widely forgotten, if it was ever known.

Bladder symptoms, constipation, and other effects are often distressing. We use Urecholine (5 to 10 mg. four times a day) or Myastenol (2.5 to 5 mg. three times a day) to aid in their correction.

Since hexamethonium is largely excreted by filtration through the kidneys, reduced renal function is another indication for great care in its use.

It is hardly any secret that we have viewed the widespread use of this drug, even under carefully controlled circumstance, with some dismay. Certainly it, along with other drugs, is useful in the treatment of emergencies of hypertensive patients but how much of a place it will have in day to day treatment I am not so certain as others. It is a pity that in this country the results of weeks or at most months of study have been published as though they were adequate evidence on which to evaluate the drug.

A PHYSICIAN: Would you give more of the details of your method of treatment with hexamethonium administered parenterally? What is the beginning dosage? How rapidly does one increase the amount? How often each day should it be given? Do you consider that in general the use of hexamethonium is the best method of treatment of hypertension?

DR. PAGE: We think it better not to give any hard and fast rules for the dosage of hexamethonium. When it is to be started parenterally, enough is given by infusion to reduce the supine pressure to the desired level. This is the starting dose given usually

every 12 hours. It may have to be raised rapidly.

The drug is given two to three times daily by subcutaneous injection or orally three to four times. It is a dangerous drug if only for the orthostatic hypotension it produces. The amount required varies over a period of weeks and months so that constant readjustment is necessary if a really satisfactory supine blood pressure level is to be achieved. I have noticed that many practitioners are using such small amounts that no side effects occur, nor is there any really significant fall in arterial pressure.

We are currently investigating another blocking agent, Pendiomid. So far our results suggest that it has only slightly less marked parasympathetic side effects while lowering arterial pressure. Like hexamethonium, when taken carelessly, it can produce dangerous collapse.

Summing up, then, I believe the ganglion blocking agents to be of great theoretic interest and of some practical value in treatment. But these drugs are dangerous and unusually difficult to regulate. After more than two years study we are not convinced that the long term results will compare favorably with those obtained by careful treatment with the drug in the first few months. Therefore a current belief that hexamethonium is alone a practical treatment of hypertension in the majority of hypertensive patients seems an exaggeration. There are many other aspects of the blocking agents that are of interest but our time is running out. The second drug to be considered is hydrazinophthalazine, or Apresoline. Perhaps Dr. Taylor will discuss its use.

DR. TAYLOR: There is increasing evidence that Apresoline blocks one of the pressor mechanisms believed to participate in many patients with essential hypertension. Further, since 60 per cent of our hypertensive patients respond at least somewhat favorably, we feel that most patients with advancing vascular disease and hypertension should have a trial with this drug. We define an adequate trial as a period of at least eight weeks during which the patient receives 200 mg. four times a day. To minimize the unpleasant side reactions, which are transiently present in 70 per cent of patients, dosage is increased slowly from 25 mg. four times a day to the higher levels. The patient's distress can be made more tolerable by reassurance that symptoms are usually not permanent. Antihistaminic drugs, analgesics and sedatives also are helpful.

Among patients with evidence of hypertensive or arteriosclerotic heart disease, restriction of dietary sodium, digitalis and gradual reduction of blood pressure will guard against congestive failure and coronary insufficiency.

A PHYSICIAN: Dr. Taylor, would you give me some more specific information about the use of antihistaminic drugs, analgesics and sedatives? There seems to be a general feeling that Apresoline cannot be taken by a substantial proportion of patients.

DR. TAYLOR: We use Benadryl in 25 to 50 mg. amounts, or Pyribenzamine in 50 mg. doses, with each dose of Apresoline. When fever, joint pains and muscle aches occur, aspirin (0.6 to 1.0 Gm.) is given with the Apresoline. Phenobarbital 32 to 50 mg. seems to modify favorably the gastrointestinal symptoms. What you mean by a "substantial number" not being able to take Apresoline depends on the criteria selected for intolerance. Seventy per cent of those who take the drug have some side reactions but less than 10 per cent find them intolerable. Another 10 per cent continue to have mild symptoms but not severe enough to prevent continuing treatment. The 30 per cent of patients who have no symptoms and the remainder who become adjusted to the drugs hardly constitutes a "substantial proportion" of patients who cannot tolerate Apresoline.

A PHYSICIAN: Dr. Taylor, you have not said anything about the use of the veratrum preparations, such as Veriloid and protoveratrine, nor have you mentioned potassium sulfocyanate. Would you give us your opinion about these preparations?

DR. TAYLOR: There is much evidence from our laboratory that veratrum alkaloids elicit hypotension by a mechanism somewhat similar to that of Apresoline. Unfortunately, the nausea producing and therapeutic doses are so

close that it is only in the exceptional patient that significant, long lasting reduction of arterial pressure is achieved. In our series of several hundred patients, only three could take the drug in amounts sufficient to lower average blood pressure and not induce vomiting. The long term results also have not been especially encouraging. Our experience with protoveratrine is that the results do not differ greatly from those of Veriloid itself.

A PHYSICIAN: Dr. Page, would you give us your opinion about the use of thiocyanate, and sodium nitroprusside. I believe you introduced the latter drug several years ago.

DR. PAGE: As I have pointed out many times, thiocyanate often is a sovereign drug for treatment of intractable hypertensive headaches. Treatment may be started with an initial intravenous dose of 1.5 Gm. of the sodium salt and then the blood level kept at from 3 to 5 mg. by oral thiocyanate when headache alone is being treated. If the hypotensive effect is also desired then the level in the blood should be raised to 8 to 12 mg. per 100 ml. It is essential that the amount in the blood be measured at regular intervals if the drug is to be used. Guessing the blood level is courting disaster!

Sodium nitroprusside is slowly converted in the blood to thiocyanate, hence the dosage can be followed by blood thiocyanate determinations. For the best results, we try to attain levels of 12 to 15 mg. per 100 ml. For acute episodes of encephalopathy, or great rises in arterial pressure, it may be given by intravenous drip, the amount given depending on the level of pressure desired. It is given orally in capsules (30 mg. four times a day) and in some patients average arterial pressure is reduced when other drugs have failed. It is another drug which requires much more study and chemical modification to determine if it can or cannot be improved.

And lastly, lumbodorsal sympathectomy should be considered. Though it is an old treatment relative to the rush and trouble of modern research, it has been used for only some 20 years. Some of you remember the bitterness with which most of this early work was greeted. Some of it was bad work, but not all of it. I think we should not forget the part played by the team of Alfred Adson, now deceased, and Edgar Allen. They were the pioneers and shared their early meager knowledge freely with the rest of us. While we no longer do many sympathectomies at the Clinic, still my opinion is that the operation is often very valuable. Dr. Corcoran, who has been so long associated with this work, has held some strong views on sympathectomy and will be glad, I am sure, to present them to you. Incidentally, I should point out that his measurements of renal blood flow before and after sympathectomy were the first to be done, and showed that renal ischemia was not relieved by the operation. Even when, for one reason or another, a pre-existing ischemia was abolished, there was no obligatory fall in blood pressure.

DR. CORCORAN: Those few measurements indicated that lumbodorsal sympathectomy did not necessarily increase renal blood flow or relieve "renal ischemia." Many measurements have confirmed this. However, one should not overlook the occasional patient in whom sympathectomy has greatly relieved hypertension, remitted the progress of nephrosclerosis and resulted in decreased renal vascular resistance.

As you suggested earlier, Dr. Page, the problem is basically one of selection. When once we find a means of detecting the 10 per cent who will respond dramatically and persistently to the operation, it will be a great day for patients and surgeons alike. Until then, both are bound to meet disappointments; surgeons are congenital optimists, so they are the less affected; the internists see the disappointing results.

As a generalization then, until such means are found, the operation can only be justified in very special situations, largely because with diet, Apresoline and methonium we have available means of treatment which are less expensive, less traumatic, more certain. There is also the possibility that other still better nonsurgical procedures will come out of the laboratories into the clinics.

Your and Dr. McCubbin's proposed mode of selection for sympathectomy by demonstration

of repetitive deep depressor responses to tetraethylammonium chloride has unfortunately never been adequately tested. I wish someone would do that. But, as I suggest, with the means now available for the relief of hypertension, I doubt that we would be justified in advising sympathectomy for this reason alone.

A PHYSICIAN: Dr. Page, one of the most difficult decisions concerns the type of treatment one will use when a patient with hypertension comes under his care. Do you have any ideas about the kind of patients whose blood pressure will respond most satisfactorily to a specific medication or do you have to determine the response by trial? I think it would help those of us who have not had the great experience that you and your associates have had in the treatment of hypertension if you would outline your plans of treatment for the patient whose case history was presented earlier in this conference.

DR. PAGE: You have touched on one of the most important problems in the field of hypertension. I know of no method short of trial to select those patients who will respond to a particular treatment. Think what it would mean if a 95 per cent success was achieved after proper selection for sympathectomy. This is one of the more important practical reasons why the various mechanisms of this clinical mosaic need be understood.

The best we can now do is to determine the rate at which vascular disease is advancing and then decide whether a more or less drastic regimen is to be recommended. In the particular patient presented this morning, we would first put him on a low-salt diet, then give Apresoline. If he failed to respond to the latter, hexamethonium would be tried and lastly, sympathectomy.

I think you will all realize that both from the diagnostic and the therapeutic viewpoint, advances have been made in the past decade. The old nihilistic approach has given way to a wave of optimism, and, I am glad to say, investigation of high order. But there is still much to be done, and we had all best get on with it by less talk and more work.

CLINICAL PROGRESS

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The Management of Congestive Heart Failure

By HERRMAN L. BLUMGART, M.D.

TO CONTROL edema of congestive failure effectively, treatment must be directed at correction of the basic fundamental derangements. Modern investigators, using improved technics, including cardiac catheterization, have shown conclusively that the central fault in congestive heart failure lies in the heart.[1, 14] Myocardial weakness, manifested by inadequate myocardial contractility, initiates the train of events of congestive failure. Within wide limits the right and left ventricles are able to receive increased amounts of blood during diastolic filling and to expel the increased amounts into the pulmonic and systemic circuits. With the inception of heart failure, the ventricle fails to empty adequately during systole. This failure to empty adequately is "forward failure." The residual blood in the ventricle at the conclusion of systole hinders diastolic filling. The blood accumulates in the auricles, in the pulmonic and systemic veins and in the lungs. This backward accumulation is "backward failure." Thus, the failure of the ventricles to empty adequately leads simultaneously to both "forward failure" and "backward failure."

General Measures

The edema of congestive failure can be affected favorably by the following: rest, digitalis, diuretics, salt balance, water regulation, sedation and removal of edema fluid by paracentesis.

Rest continues to be a fundamentally important therapeutic principle in the treatment of congestive failure. Attention to emotional as well as physical factors in attainment of rest is essential. The degree of therapeutic gain obtained through rest is proportional to the reduction of bodily activity. Usually the maximum benefit is derived from complete bed rest in semirecumbent or sitting position with occasional use of a commode at the bedside. The metabolic requirements of the body are reduced. The work of the heart is lessened. The ventricular rate is lowered. The pulse deficit may be markedly diminished. Cardiac efficiency is increased. Through this measure alone dyspnea and cyanosis are favorably affected, and at times marked diuresis occurs. This diuresis is physiologic; isotonicity of body fluids is maintained without preponderant loss of cations or anions.

Digitalis is the most important drug in the management of congestive failure for it tends to correct the fundamental weakness of cardiac contraction which gives rise, for example, to edema and dyspnea. The vigor of cardiac systole is increased, dilatation of the heart is lessened, the work output in terms of oxygen consumption, that is, "cardiac efficiency," is heightened.

Many satisfactory preparations are now available. Qualitatively, the action of the various digitalis glycosides and the margin between the therapeutic and toxic ranges of doses are similar. The physician is well advised to select one or two preparations and through continued use, to become thoroughly familiar with their pharmacologic characteristics under

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varied circumstances in many patients. A long-acting preparation, a short-acting preparation and one that is suitable for emergency intravenous use are required.

Digitoxin is generally regarded as the long-acting drug of choice.[7] Standardization is more accurate and potency more uniform than that of digitalis folia. Gastric irritation is less, absorption is more complete and rapid, and the cost to the patient is only very slightly more than that of the leaf. When given by mouth, the action of digitoxin is usually discernible within 30 minutes; the maximum effect is achieved within six to eight hours. The therapeutic–toxic ratio is approximately that of digitalis folia. The lessened gastric irritation of digitoxin has led to renewed interest in attempts at single dose digitalization and, at times, inadvertent administration of larger doses with resultant increase of cardiac and other major manifestations of digitalis toxicity. Digitoxin is available in 0.05 mg., 0.1 mg., 0.15 mg. and 0.2 mg. tablets which are roughly equivalent to 0.05 Gm., 0.1 Gm., 0.15 Gm. and 0.2 Gm. of whole leaf digitalis; a ratio of 1 to 1000.

The average "digitalizing" dose for the hypothetical patient of 70 kilos (154 pounds) is 1.2 mg. of digitoxin. Those patients, however, who require less than this amount, will experience serious toxicity from this dose. Some require two or even three times the average dose to secure the therapeutic effects. For most patients determination of the proper dose of digitalis, in whatever form it is used, must be in accordance with the classic dictum of Withering: " . . . let it be continued until it either acts on the kidneys, the stomach, the pulse, or the bowels; let it be stopped upon the first appearance of any one of these effects." In actual practice, aversion to food is usually the signal to be heeded, making unnecessary the more serious and distressing manifestations of digitalis intoxication. The risk of overdigitalization must, under certain circumstances be taken although occasional instances have been reported in which the first sign of overdigitalization was serious or even fatal toxicity.

In a patient who has not had any digitalis preparation for 10 days and who is not in emergency status, administration of 0.4 mg. as an initial dose is recommended. Subsequent doses of 0.2 to 0.4 mg. may be given at 4 to 12 hour intervals depending on the urgency of the situation, the body weight of the patient and the therapeutic response. If the patient shows auricular fibrillation, quite precise guides are afforded by the pulse deficit and the ventricular rate. Following digitalization, the maintenance dose must be determined. Some patients require 0.1 mg. daily, others as much as 0.3 mg. Therapeutic response is gauged by improvement in clinical signs and symptoms, particularly diuresis, lessening of venous distention, of dyspnea, cyanosis, and lowered heart rate. In occasional instances, observation of the characteristic electrocardiographic changes due to digitalis may be additional evidence of partial digitalization.

In emergency situations, where rapid digitalization is indicated, and, particularly if one is not certain of the exact prior digitalization of the patient, a short acting preparation such as lanatoside C, or Digoxin or ouabain is indicated. Lanatoside C in a dose of 0.8 mg. may be given intravenously followed by 0.4 mg. every two to six hours for two or three doses until the maximum therapeutic effect is achieved. The average total dosage is approximately 1.4 mg. Its duration of action is approximately 12 to 36 hours. Similarly, Digoxin may be given in an initial dose of 0.5 mg. followed by 0.25 mg. every hour. The average total dose is approximately 1.5 mg.

In general, intramuscular administration is not advisable. Absorption in the presence of congestive failure is uncertain; local irritation may ensue. Except in emergency situations, oral administration of digitoxin satisfies the requirements.

Sedation is usually accomplished by using Meperidine, one of the barbiturates, or chloral hydrate. The sodium salts of the barbiturates and of other drugs should not be used in patients on low salt intake. Morphine or its equivalents generally should be avoided because of its depressant effect on respiration

and the cough reflex, except in certain conditions such as pulmonary edema. In the presence of marked pulmonary emphysema its use is dangerous.

Oxygen Therapy by mask, tent or nasal catheter is advantageous. The choice of the method of administration will be influenced greatly by availability and by the reaction of the patient. Some patients manifest increased dyspnea, restlessness, and hyperventilation with a mask. In patients with pulmonary emphysema and with marked cyanosis, oxygen in high concentrations such as 90 per cent may remove the anoxic stimulus to respiration and thereby induce respiratory depression, coma or even death.[9]

Diuretics, Salt and Water Balances. Consideration must now be given to our treatment of the edema itself. Arrangements are made to estimate the degree to which the patient will lose his edema in response to therapy. The simplest and most accurate measure is determination of his weight after urination and before breakfast each morning. This daily weight should be charted. Fluid intake and urinary output measurements are desirable but not essential. In the presence of congestion, susceptibility to pulmonary and other infections is increased. Procaine penicillin may be given prophylactically intramuscularly at 12 or 24 hour intervals in doses of 300,000 units.

Although a full discussion of the pathogenesis of edema is not feasible in this place, certain cardinal facts must be borne in mind. As previously stated, inadequate forward flow and backward accumulation with its increased venous distention and pressure predispose to accumulation of water and electrolytes in all the tissues of the body. The effects of these abnormal hemodynamics are particularly important on the kidneys; the renal factor in congestive failure is of decisive importance. When the output of blood to the tissues is reduced, the amount delivered to the kidney is lowered disproportionately to that of the rest of the body.[14] Stasis occurs also in the veins of the kidneys. The amount of the glomerular filtrate is markedly reduced. As this reduced amount of glomerular filtrate descends to the tubules, a greater than normal reabsorption of fixed base, such as sodium, and of water back into the blood stream, occurs.

The lowered glomerular filtration and increased tubular reabsorption are of cardinal importance in the pathogenesis of congestive failure and demand therapeutic correction. Digitalis promotes increased blood flow and glomerular filtration; diuretics lessen tubular reabsorption.

A lowered salt intake is prescribed. Initially, particularly if the patient is obese or well nourished, a simple dietary regimen of four to six glasses of milk, that is, 1000 to 1500 cc. of milk daily may be employed. Approximately 1000 to 1500 calories and from 500 to 750 mg. of sodium are thus administered. A more limited sodium intake of 200 to 500 mg. is not infrequently necessary. Diets low in salt and containing more adequate calories and vitamins and other essentials may be prescribed according to the individual needs of the patient by utilizing the diets made available in the American Heart Association's "Recipes for a Low Salt Diet." More liberal amounts of sodium chloride, up to 2 to 3 Gm., occasionally may be permissible in order to maintain nutrition, particularly if malnutrition and hypoproteinuria are present. Supplementary vitamins and increase in dietary protein are frequently advisable.

Water, sufficient to keep the patient comfortable, is permitted on the regimen of restricted salt intake. Usually up to 2000 or 3000 cc. of water is allowed; marked restriction is unnecessary and undesirable; large amounts of 6 or more liters, as have occasionally been advocated, probably accomplish little and entail certain risks.

Diuretics. The mercurial diuretics are usually essential in the control of edema. The xanthine diuretics are relatively weak and only occasionally useful by mouth as adjuncts in prolonging the interval between injection. The calcium rather than the sodium salts should be used for this purpose. One of the mercurial preparations containing mercury organically bound with theophylline in a dose of 2 cc. should be given deeply intramuscularly. Ad-

ministration early in the morning is advisable in order to obtain diuresis predominantly during the day. If the reaction of the patient is unknown, an initial dose of 0.5 or 1 cc. should be given. In patients with poor absorption in edematous areas, the use of mercaptomerin (Thiomerin) which can be injected into the deltoid, is desirable. This drug may be used subcutaneously and is attended by less pain and can be self administered by the patient regularly if necessary. Prior preparation of the patient over one or more days by the daily administration of 3 to 4 Gm. of enteric coated but absorbable ammonium chloride enhances the effects of the mercury diuretics. In some patients the frequency of injections can be reduced by administering ammonium chloride intermittently, that is, three or four days in succession each week. Overdosage induces gastrointestinal symptoms and chloride retention with acidosis.[13]

Some patients exhibit sensitivity or idiosyncracy to the mercurial diuretics. Pruritis, skin rashes, stomatitis, metallic taste, gastrointestinal disturbances, prolonged local pain and induration at the site of injection may be encountered. These untoward reactions are frequently obviated by shifting to a different preparation and to smaller doses. The antihistaminic drugs are at times effective in ameliorating the skin manifestations. British anti-Lewisite (BAL) may be used in the treatment of the toxic manifestations but should not be used simultaneously with the mercurials since it blocks the renal tubular diuretic action.

Management of the Clinical Course

Let us, at this point, return to our patient and assume that he has been comfortably settled in bed or in a chair, depending on his comfort. If our physical examination reveals dyspnea and respiratory embarrassment due to pleural effusion or ascites, paracentesis is indicated with the use of liberal amounts of procaine and a 16 or 18 gage needle. If the patient is seriously ill, if the venous pressure as indicated by venous engorgement of the cervical and other veins is high, if cyanosis is prominent and the hemoglobin normal or elevated, phlebotomy of 250 to 500 cc. may be indicated. Phlebotomy may occasionally be contraindicated in a patient with cor pulmonale and secondary compensatory polycythemia.

The use of a commode or bathroom privileges is permitted if the patient is equal to the effort. After the inauguration of rest, digitalis, diuretics, diet, sedation, and oxygen therapy, as indicated by the initial appraisal of the patient's condition, the therapeutic regimen will be modified, adjusted, or amplified to meet the needs of the individual patient.

The chief guide in fashioning the optimum regimen is the response of clinical evidences of congestive failure to treatment; the daily weight and urinary output are of particular importance. Vital capacity determinations may be helpful in patients suffering primarily from pulmonary congestion. If massive edema is present, a daily loss of body weight of 2 to 4 pounds (1 to 2 Kg.) is preferable to inordinately large diureses of body fluid. Particularly in elderly males, large diuresis may lead to acute distention of the bladder and urinary retention. Sudden loss of large volumes of edema fluid may be attended by loss of considerable fixed base including sodium, potassium and calcium.[11] Muscle cramps, marked weakness, nausea, vomiting may only add to the patient's woes. Predisposition to pulmonary infarction has also been reported under such circumstances. If the discomfort is considerable and is clearly due to inordinate diuresis, the administration of 1 to 2 Gm. of sodium chloride by mouth is to be considered or parenterally if nausea is present. In occasional patients who experience nausea after mercurial diuretics, orange juice or potassium chloride or citrate by mouth in doses of 1 to 2 Gm. administered during the 24 hours after injection may be helpful.

In most cases, the administration of 1 or 2 cc. of the mercurial diuretic producing a loss of 3 to 4 pounds should be given every other day for two to four doses, with one of the acidifying salts, in addition, if necessary. When all signs of edema have disappeared and the weight reaches a resistant level, the "dry weight" of the patient has been attained. The interval between doses may then be lengthened by one or two days if not more than 2

pounds are regained in the next 48 hours. Every effort should be made to maintain the patient at about his dry weight. During long term care of chronically ill patients, the dry weight may slowly and gradually lessen due to cachexia; unrecognized extracellular fluid may accumulate. Therefore, the true dry weight should be re-evaluated every several months. The amount of reaccumulation should not exceed that which can be removed by a single administration of 1 or 2 cc. of a mercurial diuretic. In the course of time, liberalization of the diet is often feasible without increasing the frequency of mercurials. The use of salt substitutes enhances the palatability of the diet to some patients. Other condiments without sodium, such as pepper, paprika, mustard leaves, vinegar, cinnamon, garlic are permissable and very helpful.

It is important not to administer a mercurial diuretic in the presence of active nephritis. This may at times be difficult to determine, particularly since albuminuria, casts, white cells and red cells in the sediment, and azotemia with the nonprotein nitrogen as high as 70 or 80 mg. per 100 cc. occurs in congestive failure in the absence of significant intrinsic renal disease. When the nonprotein nitrogen blood level reaches 60 or 70 mg. per 100 cc. the possibility of intrinsic renal disease must be seriously considered. The specific gravity of the urine may be a helpful guide. A high specific gravity favors congestive failure while a low specific gravity of 1.012 or less in the presence of oliguria raises the suspicion of significant renal pathology. Occasionally, it is impossible to rule out the presence of significant underlying nephritis. Under such circumstances small doses of a mercurial diuretic such as 0.5 cc. may be given and the effects noted on urine output during the ensuing 12 hours as well as on the body weight the next morning. It must be remembered that in the absence of a therapeutic response to mercurial diuretics in patients with congestive failure, toxic accumulation is prone to occur. The use of the xanthines as a diuretic is also to be considered under such circumstances, that is, 0.5 or 1 Gm. of aminophylline by mouth or by suppository. The calcium salt (Theocalcin) 0.5 Gm. four doses daily may be better tolerated and more effective in some patients. In comparison with the mercurial diuretics, the xanthine diuretics are less potent and more irregular in action.

The use of mercurial diuretics by mouth to maintain dry weight has been rather extensively studied and is advocated by some. The results are gratifying in some patients, reduce the frequency of parenteral injections or permit somewhat more liberal sodium intake with more nutritious diet. But even in those patients who tolerate such regimens satisfactorily for many weeks, the appearance of gastrointestinal symptoms—nausea, vomiting, abdominal cramps—of renal irritation and, occasionally, of serious mercury poisoning and renal damage have prevented widespread adoption of this method of therapy. Mercurial preparations by mouth should be given on an intermittent schedule such as three, four, five days a week or three weeks in each month to avoid accumulation of mercury. They should not be used if intrinsic renal disease is present. New preparations are available but their value has not been thoroughly appraised as yet.

In general, our objective is to maintain the patient at "dry weight" on as comfortable a regimen of diet, diuretics, and daily activity as possible. The daily weight is the guiding point of reference. To rely on recrudescence of dyspnea or edema of the legs or right upper quadrant distress is analogous to treating a diabetic with insulin only when he becomes acidotic or shows marked glycosuria. Patients may gain more than 5 or 10 pounds of edema fluid before edema of the legs or rales in the lungs become manifest. To determine the optimal regimen for a particular patient requires skill in balancing the various measures according to his individual needs. Thus, a more liberal diet or increased activity may be required by some patients with more frequent injections of diuretics or with reinforcement by the acidifying salts such as ammonium chloride. The use of enteric coated 1 Gm. tablets facilitates tolerance of higher, more effective doses such as 6 Gm. daily; 3 to 4 Gm. are, however, generally sufficient.

During the past few years, the use of cation exchange resins has received considerable study.

This ingenious therapy in usual dosage eliminates 2 to 4 Gm. of sodium daily via the gastrointestinal tract and consequently permits less frequent injections of diuretics. Enthusiasm for this therapeutic adjunct is waning, however. The percentage of sodium removed at higher levels of sodium intake is less than at lower levels. The resins cannot be relied upon to permit a free use of salt. The preparations are unpalatable for many patients and occasion gastrointestinal distress. Of more serious moment is the difficulty of maintenance of a satisfactory regimen without occasionally encountering serious electrolyte disturbances of calcium, potassium, and sodium. If cation exchange resins are employed, the renal function of the patient should be appraised, and, if depressed, the resins should be used, if at all, only with greatest caution. In general, reliance on low salt regimens with salt substitutes and, when necessary, more frequent injections of mercurial diuretics, are preferable.

Recently the carbonic anhydrase inhibitor type of pharmaceutical has been made available. Experience is as yet too limited to permit accurate evaluation.

Acute Left Ventricular Failure

Acute Pulmonary Edema. This medical emergency occurs most commonly in patients with hypertensive heart disease. It may also occur during or after operation, particularly if saline infusions or blood transfusions have been administered rapidly or in a large quantity. Postoperative studies of the dynamics of the circulation in cardiac patients by Altschule and Gilligan[2] have shown that if physiologic saline or 5 per cent glucose in saline are given at rates below 15 cc. per minute, abnormally great or prolonged rises in venous pressure and marked increase in cardiac output or blood volume are avoided. Aside from their immediate effects, intravenous infusions that are repeated too often over a period of several days, favor the development of peripheral and pulmonary edema and cardiac pain. Paroxysmal dyspnea and cough may progress rapidly to frank pulmonary edema with intense cyanosis, struggling respiration, bubbling rhonchi and rales with the expectoration of pink, frothy sputum.

The patient should be placed in Fowler's position or allowed to sit in a chair, where he will frequently be more comfortable than in bed. If the patient is struggling and excited, morphine sulphate, 15 or 30 mg. given hypodermically, may be life-saving. If the patient has progressed to stupor, morphine should not be given. If the patient is seen earlier in the attack and the situation is urgent, morphine, 10 to 30 mg. intravenously, may be indicated. Aminophylline by slow intravenous injection of 0.25 to 0.5 Gm. may be effective in reducing bronchial spasm.

If the patient has not received a digitalis preparation for 10 days, lanatoside C may be given in doses of 0.6 to 0.8 mg. intravenously, followed by 0.4 mg. at hourly intervals until a favorable response is elicited. Ouabain or Digoxin is preferred by some clinicians for rapid digitalization.

Oxygen therapy is urgently indicated. It should be given by means of an oxygen mask, metered for positive pressure if available (meter mask). A volume flow of 8 to 10 liters a minute achieves an oxygen concentration of 40 to 60 per cent. If a tent is utilized, a flow of 10 to 12 liters per minute of oxygen is necessary to attain a concentration of 50 to 60 per cent. If these methods are not available, a nasal catheter, or if the patient tolerates the procedure, double nasal catheters should be employed. The use of ethyl alcohol introduced in the oxygen line to reduce surface tension of frothy pulmonary transudate has been proposed by Luisada[15] and favorable results have been reported.

With marked peripheral venous engorgement, the rather rapid removal of 500 cc. of blood should be performed. "Bloodless phlebotomy" likewise may be effective under such circumstances. Tourniquets, preferably blood pressure cuffs, should be applied to all four extremities. Three of these cuffs are inflated at a time to a pressure slightly lower than the patient's diastolic pressure. Pressures below diastolic at levels of 20 to 30 mm. Hg may be used if the higher pressures occasion discomfort. The amount of blood trapped in the limbs is

presumably somewhat less at the lower pressures. Release of each cuff is done in rotation every 15 minutes to permit re-establishment of adequate blood flow.

Administration of a mercurial diuretic is frequently a valuable adjunct and, in the absence of contraindications, should be administered intramuscularly or subcutaneously shortly after the measures above described have been initiated.

The Refractory State

Occasionally we are confronted by the patient whose congestive failure stubbornly resists our usual therapeutic measures. The program of treatment must be carefully reviewed.[10] Before accepting the possibility of true refractoriness due to inherent, irremedial cardiac weakness we must ask ourselves the following questions.

1. *Is the Refractory State Due to Specific Etiologic Conditions which Can Be Corrected?*

Certain conditions increase the requirements of the body for blood. *Hyperthyroidism*, *anemia*, *pregnancy*, *beriberi*, *arteriovenous aneurysms*, and *certain congenital malformations* such as *patent ductus arteriosus* may be responsible for refractory congestive failure because they impose additional work on the heart. Treatment of such underlying conditions may remove the extra demand on the heart permitting the normal needs of the body to be met more adequately. *Cardiac arrhythmias* may reduce the efficiency of the heart.

Tamponade from pericardial effusion or *constrictive pericarditis* may have been overlooked.

Hypoproteinemia not infrequently predisposes to edema in cardiac patients who have been anorexic and on a low sodium diet or who have concomitant hepatic or renal disease.

Intercurrent infections have an adverse effect on the myocardium. Rheumatic fever, pulmonary and other infections must be borne in mind. The possibility of subacute or acute bacterial endocarditis particularly must be considered.

The beneficial use of the veratrum drugs to lower *hypertension* in some patients with congestive failure has been reported.

Pulmonary embolism and infarction may occasionally be responsible for refractoriness. In the presence of thrombophlebitis the use of heparin and dicumarol is indicated. The high incidence of pulmonary embolism in bedridden congestive failure patients has led some physicians to employ anticoagulant therapy in all such patients, provided, of course, no specific contraindications are present and adequate laboratory facilities are at hand.

In some patients, particularly those with acute pulmonary edema, the possibility of *painless acute myocardial infarction* must be considered.

2. *Have We Obtained the Full Benefits of Complete Digitalization?*

Underdigitalization may control the cardiac rate at rest, but may not prevent a disproportionate rise on effort. Assurance of complete digitalization is imperative in refractory cases. Therefore, digitalization to the point of toxicity, if necessary, must occasionally be undertaken despite the discomfort and risks entailed. Even slight increases in dosage such as an additional 0.1 mg. of digitoxin every other day or 0.05 mg. daily may at times achieve distinct improvement. Gitalin has been reported as a particularly effective preparation in refractory congestive failure by Hejtmancik and Herrmann.[8] The usual digitalization dosage is 6 to 7 mg., the maintenance dose 0.5 to 1 mg. Finally, it must be remembered that overdigitalization, particularly if many extrasystoles are induced, may also contribute to the refractory state.

3. *Can More Adequate Rest Be Provided?*

The judicious use of mild sedation during the day and obtaining restful nights for the patient are essential. The use of a cardiac bed permitting the equivalent of the sitting position, or providing a large chair suitably supported by pillows, 6 or 9 inch head blocks for the bed, use of the commode rather than bedpan or bathroom may promote improvement. Use of elastic stockings to decrease the discomfort of swelling and to prevent thrombo-

phlebitis is to be considered. The alleviation of anxiety, the elimination of disturbing visitors, and pleasant nursing care may enhance the patient's recovery.

4. *Have We Restricted Sodium Sufficiently?*

Congestion and edema of the lungs, abdominal viscera and extremities are consequent to increased retention of sodium by the kidneys. A more rigid dietary restriction of sodium should be attempted. The Karrell diet of 800 or 1000 cc. of milk provides 400 to 500 mg. of sodium daily and is, therefore, unsatisfactory for refractory or severely decompensated patients.

A diet containing 50 to 100 mg. of sodium daily but furnishing adequate potassium, chloride, protein and total calories may be used as a temporary expedient. The diet consists of 2000 cc. of Lonalac formula mixed well into an even suspension, flavored with vanilla and kept chilled; 400 cc. of this are given five times daily. Orange juice, 250 cc., is given twice daily. Such restriction is seldom needed for more than one week.

The use of cation-exchange resins to interfere with sodium absorption has received much study and has been discussed previously. The use of resins in refractory cases is not advised unless facilities for frequent measurements, at least weekly, of serum potassium, sodium and calcium are available. When low sodium diets, and diuretics are no longer effective, cation-exchange resins are worthy of trial. Ideal dosages of the resins have not been determined, but 15 Gm. three times daily with meals are usually administered to patients on a daily intake of 1 to 4 Gm. of sodium chloride. For most refractory patients, the use of low salt diets with or without the use of salt substitutes is safer and preferable.

5. *Has the Maximum Benefit Been Obtained from Diuretics?*

If the edema of congestive failure is refractory to diuretics, several possibilities should be considered. The absorption of the mercurial diuretic after injection into edematous areas may be unsatisfactory. The use of a less irritating diuretic such as Thiomerin into the arms or anterior thigh may be indicated. Preparation of the patient by use of one of the acidifying salts such as ammonium chloride, or the use of aminophylline by mouth or rectally, beginning a day prior and continuing on the day of injection may potentiate the effect of the mercurial diuretic. The use of xanthine diuretics or of urea by themselves is only occasionally of value under such circumstances. Insistence on bed rest 12 hours prior, and 18 hours after mercurial diuretics may increase the urinary output.

Occasionally the situation is of such urgency or the patient is sufficiently refractory to usual measures to warrant intravenous administration of diuretics which, however, on very rare occasions, causes death. If indicated, dilution of the mercurial diuretics to a volume of 20 cc. and slow administration over a period of 10 minutes should be practiced. The opinion has been expressed that the use of organic mercurials, such as mercaptomerin (Thiomerin), which do not contain theophylline, are attended with less risk of sudden death and are, therefore, preferable for intravenous use.

6. *Is the Refractory State Due to the Low Salt Syndrome or Other Electrolyte Imbalance?*

The low salt syndrome or other electrolyte imbalance should be suspected when the urinary volume is depressed, is not increased by diuretics, and the patient experiences one or more of the following symptoms: weakness, drowsiness, headache, loss of appetite, thirst, nausea, vomiting, giddiness or syncope, muscle or abdominal cramps, gain in weight, and increased heart rate.[3, 12] Cardiac psychosis may be a cardinal consequence and may be alleviated by therapy. Urinary volume is usually depressed three to five days prior to the onset of the symptoms and is associated with gain in weight and increased heart rate. These manifestations may be due to an undue loss of chlorides, of sodium, of potassium, calcium, and magnesium, or, under certain conditions such as after the administration of ammonium chloride, to retention of chloride and resultant acidosis with or without the loss of fixed base.[3, 6, 13] When refractoriness to mercurial

diuretics develops, further use should not be attempted, therefore, until possible electrolyte disturbances have been corrected and careful evaluation of the clinical state, including the kidneys, has been made.

The low salt syndrome is characterized by reduced values of serum sodium, chloride and carbon dioxide. The nonprotein nitrogen or blood urea nitrogen is elevated. The normal values of approximately 140 mEq. of sodium, 100 mEq. of chloride and 25 mEq. of carbon dioxide (50 to 60 volumes per cent) may be decidedly lowered to levels such as 125 mEq., 85 mEq. and 14 mEq. (30 volumes per cent), respectively. This syndrome may be due to the concomitant presence of salt losing nephritis or to oft repeated injections of mercurial diuretics, particularly if salt intake has been restricted, the cation exchange resins have been employed, or perspiration has been excessive. Injection of mercurial diuretics in the presence of the low salt syndrome can lead to mercurial renal poisoning with fatal results. The body fluids are hypotonic because of the preponderant excretion of salt consequent to the salt losing nephritis or to the prior mercurial diuresis. In advanced cases the prognosis is grave and shock is present. Treatment consists in the immediate replacement of salt by slow intravenous injection of 5 per cent hypertonic solution; normal saline would merely increase the edema without substantially relieving the hypotonicity of body fluids or the reduced serum electrolyte concentrations. The amount of salt administered in this manner should be calculated from the serum values after determining the magnitude of the existing deficit. The water content of the body, including intracellular and extracellular fluid, is assumed to be 70 per cent of the body weight. If the serum sodium level is reduced 10 mEq. in a patient of 75 kilograms, the sodium deficit would be 525 mEq. One hundred cubic centimeters of 5 per cent saline contains 86 mEq. of sodium and therefore approximately 600 cc. would be theoretically necessary. Approximately one half of the calculated deficit may be administered the first day. Caution must be exercised; excessive or rapid increase in extracellular fluid volume may precipitate or increase pulmonary congestion. Patients frequently show restoration of satisfactory serum values and recovery of responsiveness to diuretics after administration of less than the full calculated amounts of salt. This is not surprising for calculations are based on total body water or 70 per cent of body weight. The extracellular compartment comprising interstitial fluid and plasma constitutes 20 per cent of body weight. Because of frequently associated potassium deficit, potassium citrate or chloride may be given in daily doses of 2.6 Gm. orally.

The low chloride syndrome, that is, hypochloremic alkalosis is usually consequent to mercurial diuresis. As previously stated, mercurial diuresis is accomplished by decreased renal tubular reabsorption of chloride, sodium, and potassium with resultant loss of these ions into the urine and consequent increase in urinary volume. Usually, a greater loss of chloride than of sodium occurs.[4, 5] This results in hypochloremic alkalosis. When the plasma chloride falls from the normal of about 100 mEq. to 85 mEq., or less, per liter, tubular reabsorption of practically all the chloride occurs, diuresis is inhibited, and mercurial diuretics are ineffective. Low food intake and loss of chloride by vomiting may be important contributory factors. The presence of hypochloremic alkalosis with low serum chloride concentration is proven by demonstrating the lowered serum chloride concentration and the reciprocal high serum carbon dioxide combining power; the sodium serum concentration also is frequently reduced but may be normal. This condition can be corrected by the administration of ammonium chloride. Doses of 2.0 to 4.0 Gm. daily are usually well tolerated when given with meals; larger doses occasionally are necessary. The use of enteric coated tablets prevents nausea and vomiting, but, because of uncertainty of absorption, should whenever possible be replaced by uncoated tablets in treatment of this condition. If oral administration is not feasible, intravenous injection of not more than 200 cc. of a two per cent solution at a rate of 5 to 10 cc. per minute may be given.

The low sodium syndrome, that is, hypona-

tremic acidosis, the converse of the low chloride syndrome, likewise may prevent satisfactory diuresis. This occurs particularly in patients with renal disease and is encountered with unnecessary frequency because of the vogue of low sodium diets and vigorous mercurial diuretic therapy. Normally, anions can be excreted as ammonium salts. With renal impairment ammonia is not available; fixed base, particularly Na^+, must be used. Depletion of body sodium and, occasionally, of other fixed bases such as potassium and calcium occur. The clinical symptoms and signs of the low salt syndrome, the low urinary volume, the refractoriness to diuretics, and the presence of renal disease suggest the presence of the low sodium syndrome. The diagnosis is confirmed by finding a decrease in the serum sodium from the normal value of approximately 140 mEq. to 125 mEq. or less per liter. The blood carbon dioxide combining power is generally below 30 volumes per cent. The serum chloride is also frequently reduced but may be relatively elevated if ammonium chloride has been administered. Treatment consists in the intravenous administration of sodium bicarbonate, one sixth molar sodium lactate solution, or, at times, sodium chloride, to repair the chloride as well as the sodium deficiency. If sodium chloride is given intravenously, a 5 per cent solution is employed as previously described in an amount calculated from the serum electrolyte figures to restore the deficit. With restoration to normal values, adequate renal function and responsiveness to mercurial diuretics occur, provided irreversibility has not been induced.

Hypopotassemia and depletion of tissue potassium also may occur with or without hyponatremia. The symptoms of both conditions are similar. Hypokalemia may also occur with hypochloremia. The diagnosis is confirmed by finding the plasma potassium concentration reduced below the normal of 4 to 5 mEq. per liter or observing characteristic electrocardiographic changes. Therapeutic responsiveness to mercurial diuretics may be improved by the administration of 2 to 3 Gm. of potassium chloride or potassium citrate four times daily.

Severe hyperchloremic acidosis may be caused by the administration of ammonium chloride to patients with congestive failure and nephritis whose renal capacity to excrete a markedly acid urine is impaired.[13] Loss of fixed base as well as marked acidosis may result from the administration of 6 to 8 Gm. of ammonium chloride for seven or more days. This syndrome differs from the low salt syndrome in which acidosis is not observed and in which the serum chloride concentration is low rather than elevated. Patients with ammonium chloride acidosis may manifest lassitude or stupor, dyspnea of the Kussmaul type, very high blood chloride levels, low carbon dioxide combining power and marked azotemia. The administration of sodium bicarbonate or one-sixth molar sodium lactate solution intravenously is indicated. In the congestive failure patients reported by Sleisenger and Freedberg,[13] all of whom had intrinsic renal disease or impaired renal function, rapid improvement followed the omission of ammonium chloride, and the administration of 3 liters of one-sixth molar sodium lactate solution daily for one to three days or the use of sodium bicarbonate orally with, at times, intravenously administered 5 per cent glucose solutions. Frequent determinations of the serum carbon dioxide combining power, chlorides and nonprotein nitrogen are indicated as guides to the amount to be used and the frequency of administration.

7. *Is the Refractory State Due to Nutritional Deficiency?*

Anorexia, particularly on a limited dietary regimen, may lead to various deficiencies. Beriberi heart disease may insidiously develop and be responsible for refractoriness. Thiamin administration may initiate improvement. Other vitamin deficiencies may be induced by loss of water-soluble vitamins during diuresis. Similarly low protein content of the diet, loss of protein in the urine or in chest and abdominal fluids, and the hepatic dysfunction intrinsic in congestive failure may lead to hypoproteinemia. This may be exaggerated by the hypervolemia which further reduces the protein concentration. The use of serum albumin, protein hydrolysates low in sodium, plasma or blood is indicated but

usually the results are disappointing; prevention is of far greater importance.

8. *Are Mechanical, Surgical or Other Measures Indicated?*

Thoracentesis and abdominal paracentesis may at times greatly enhance diuresis and hasten convalescence. Large quantities of subcutaneous edema may be drained by inserting Southey tubes or 14 gage needles into the subcutaneous tissues above the ankle. After a few minutes the needles may be removed. Loose dressings may be applied to soak up the edema fluid or it may be permitted to drain freely into a receptacle. Procaine penicillin 300,000 units should be injected intramuscularly once or twice daily to prevent infection. When repeated drainage of large amounts of edema fluid is practiced, the concomitant loss of protein should be borne in mind. Less frequent removal or increasing the dietary protein intake may be indicated.

The present day surgical approach of commissurotomy in advanced mitral stenosis offers certain suitable patients striking relief. Lowering of the metabolic rate and hence the body requirements for blood by depressing thyroid function by the use of radioactive iodine may induce improvement in some patients. Favorable results have been reported by Jaffee[16] Wolferth and associates[17] and the author and his associates.

Conclusion

This discussion of congestive failure differs from that of the previous decade in several important respects. It has become generally acknowledged that the reduction of sodium chloride to 2 Gm. per 24 hours is inadequate in many patients and that diets containing 200 mg. or less of sodium are practical. The old Karrell diet of 200 cc. of milk four or five times per day contains about 800 to 1000 mg. of sodium chloride and is not the best diet for the severe forms of congestive failure over prolonged periods of time.

In the years of fluid restriction without salt restriction, patients were miserable from thirst. It is now recognized that with proper restriction of salt the patient may be permitted enough water to ensure comfort. Although some have advocated forcing fluids to levels as high as 5000 and 6000 cc. per day, the value of such a regimen is doubtful.

The modern regimen of salt restriction and mercurial diuretics has resulted in improved management of congestive heart failure, lessened disability, and greater longevity. But the use of a powerful tool such as marked sodium restriction also has introduced dangers. Sodium depletion and other electrolyte imbalance, particularly in patients with renal disease who are placed on a rigidly restricted sodium intake, has led to the development of weakness, anuria, and azotemia, which, when unrecognized, has resulted in fatalities. The use of mercurial diuretic agents in such patients has heightened the incidence of such reactions. In other patients with renal impairment, mercurial diuresis has resulted in a disproportionate loss of chloride with hypochloremic alkalosis. These untoward complications may, however, be avoided by awareness of their occurrence, early diagnosis and immediate correction of the electrolyte imbalance.

References

[1] Altschule, M. D.: Physiology in Diseases of the Heart and Lungs. Cambridge, Mass., Harvard University Press, 1949.

[2] — and Gilligan, D. R.: The effects on the cardiovascular system of fluids administered intravenously in man. II. The dynamics of the circulation. J. Clin. Investigation **17:** 401, 1938.

[3] Bland, J. H.: The Clinical Use of Fluid and Electrolyte. Philadelphia, Saunders, 1952.

[4] Blumgart, H. L., Gilligan, D. R., Levy, R. F., Brown, M. G., and Volk, M. C.: Actions of diuretic drugs. I. Action in normal persons. Arch. Int. Med. **54:** 40, 1934.

[5] —, —, and Volk, M. C.: Action of Diuretic Drugs. II. Effect of Diuretic Drugs on the Acid-Base Equilibrium of the Blood in Patients with Cardiac Edema. Medical Papers Dedicated to Dr. Hanry Asbury Christian. Baltimore, Waverly Press, 1936. P. 191.

[6] Gamble, J. L.: Chemical Anatomy, Physiology and Pathology of Extracellular Fluid. Cambridge, Mass., Harvard University Press. 1947.

[7] Gold, H., Kwit, N. T., Modell, W., Hanlon, L. W., Kramer, M., Greenberg, S., Otto, H. L., Cotlove, E. W., Benton, J. D., Pearlmutter, M., and Zahm, W.: A system for the routine treatment of the failing heart. Am. J. Med. **3:** 665, 1947.

[8] Hejtmancik, M. R., and Herrmann, G. R.: A clinical study of Gitalin. Arch. Int. Med. **90:** 224, 1952.

[9] Mithoefer, J. C.: Increased intracranial pressure in emphysema caused by oxygen inhalation. J.A.M.A. **149:** 1120, 1952.

[10] Myers, G. B., Hellems, H. K., Iseri, L. T., and Boyle, A. J.: Treatment of congestive failure refractory to the standard regimen. J. Michigan M. Soc. **49:** 1434, 1950.

[11] Ray, C. T., and Burch, G. E.: Clinical aspects of mercurial diuretics. Circulation **3:** 926, 1951.

[12] Schroeder, H. A.: Use of diuretic agents. J.A.M.A. **147:** 1109, 1951.

[13] Sleisenger, M. H., and Freedberg, A. S.: Ammonium chloride acidosis; a report of six cases. Circulation **3:** 837, 1951.

[14] Stead, E. A., Jr.: Role of cardiac output in mechanisms of congestive heart failure. Am. J. Med. **6:** 232, 1949.

[15] Luisada, A. A.: Therapy of paroxysmal pulmonary edema by antifoaming agents. Circulation **2:** 872, 1950.

[16] Jaffe, H. L.: The multiple small dose radioiodine technic for the treatment of severe euthyroid cardiac disease. Ann. West. Med. & Surg. **5:** 4, 1951.

[17] Wolferth, C. C., Chamberlain, R. H., and Mead, J. J.: Radioactive iodine in the treatment of angina pectoris. Pennsylvania M. J. **54:** 352, 1951.

ABSTRACTS

BLOOD COAGULATION

Svihla, A., Bowman, H., and Ritenour, R.: Relation of Prothrombin to the Prolongation of Clotting Time in Aestivating Ground Squirrels. Science **115:** 306 (March 21), 1952.

Ground squirrels were found to have a change in blood clotting time when these mammals were in the dormant state during either estivation or hibernation. Using a modified Quick method, the prothrombin content in the blood of dormant squirrels was found to be significantly reduced. The clotting time for active animals with undiluted blood was 19.5 seconds as compared to 23.3 seconds in the dormant animals. With progressive dilution of the blood, the differences became more significant, so that at 10 per cent dilution the clotting time was 76.5 seconds in the active animals as compared with 174.1 seconds in the dormant. A decrease in the amount of prothrombin during dormancy alleviates the danger of thrombus formation due to the slower rate of circulation.

WAIFE

McDevitt, E., Huebner, R. D., and Wright, I. S.: Ineffectiveness of Heparin by Sublingual Administration. J.A.M.A. **148:** 1123 (March 29), 1952.

Heparin was administered sublingually 29 times to 15 persons. Nine different lots of heparin from four pharmaceutical companies were studied. It was not possible to confirm the findings of Litwins and associates regarding the effectiveness of the sublingual administration of heparin preparations now available. The authors found that in some instances the clotting times were slightly shortened and in others slightly prolonged, but the prolongation of clotting time in any case was not sufficient to be of therapeutic significance.

KITCHELL

CONGENITAL ANOMALIES

Benchimol, A. B., and Fraga Filho, C.: Single Ventricle. O Hospital (March), 1952.

The authors report a case of "cor triloculare biatrium," with autopsy confirmation. The unusual feature of this case was a long survival with absence of heart failure to the age of 25, when cardiac decompensation occurred in the seventh month of pregnancy. There was no cyanosis at rest, and there were typical signs of mitral stenosis which led to the incorrect diagnosis of this valvular lesion, such as occurred in the case described by Paul White and associates.

SCHLESINGER

Gibson, S., and Lewis, K. C.: Congenital Heart Disease following Maternal Rubella during Pregnancy. Am. J. Dis. Child. **83:** 317 (March), 1952.

The authors reviewed the records of 1366 private patients and found a history of maternal rubella in 17, or approximately 1 per cent. Of the 17 patients whose mothers had measles, 14 were thought to have a patent ductus arteriosus. The diagnosis was confirmed by operation in 10 of these cases. In these 10 patients, four were found to have an additional cardiac defect.

In a review of 140 cases of patent ductus arteriosus in otherwise healthy children, only six cases were found in which a significant murmur persisted after the ductus had been severed (incidence, 4.3 per cent). The authors state that the finding of an additional lesion in 4 of 10 cases of proved patent ductus

arteriosus following maternal rubella at least suggests that complicating lesions are much more frequent in these patients than in otherwise normal children.

MARGOLIES

Storstein, O., Humerfelt, S., Muller, O., and Rasmussen, H.: Studies in Catheterization of the Heart in Cases of Patent Ductus Arteriosus Botalli. Acta med. scandinav. **141:** 419 (March), 1952.

This report is concerned with studies made in 21 cases of patent ductus arteriosus, 16 of whom were operated upon subsequently. A typical machinery murmur was present in 18 cases; two patients had a loud systolic murmur and a very weak diastolic murmur without the typical machinery character; and one patient had only a systolic murmur in the second and third intercostal space at the left sternal border. A systolic murmur of grade II to V intensity was present at the apex in 19 patients; and in five patients there was a low-pitched short diastolic and presystolic murmur at the apex similar to that of mitral stenosis. The electrocardiogram was normal in 18 cases, two patients had atypical right retardation, and one had auricular fibrillation. The pressure in the pulmonary artery was found to be abnormally high in 7 out of 13 cases, while 9 out of 15 cases showed an abnormally high pressure in the right ventricle. The right auricular pressure was normal in all cases. The size of the shunt ranged from 1 to 18 L. per minute, or from 19 to 72 per cent of the total blood flow through the lungs. A rough calculation of the work of the heart in this condition is reported to indicate that a patent ductus increases the work of the right ventricle by 70 per cent and that of the left ventricle by 130 per cent. When there is considerable pulmonary hypertension, the work of the right ventricle is even greater.

ROSENBAUM

Busch, F.: Roentgen Examination in Coarctation of the Aorta. Acta Radiol. **37:** 216 (March–April), 1952.

In six of seven cases of coarctation of the aorta, the diagnosis was confirmed by roentgenologic methods. In three, planigraphy (tomography) indicated the site of stenosis. In one kymography helped. Three patients had adequate visualization of the site of coarctation by means of conventional angiocardiography. One patient was subjected to the passage of a catheter up the cubital artery on the left side, but the catheter passed into the carotid artery where it was held up and the examination was interrupted. The author cites a one per cent mortality in the catheter procedure and apparently feels that this procedure is not justified.

SCHWEDEL

Segers, M., and Brombart, M.: Multiple Indentations of the Esophagus in Coarctation of the Aorta. Acta Cardiol. **7:** 357 (Fasc. 3), 1952.

In a 45 year old man with typical coarctation of the aorta, the authors found at fluoroscopy in both oblique diameters multiple indentations of the barium filled esophagus which could not be related to peristaltic waves, since they remained constant in size and localization and showed distinct pulsations. They had to be ascribed to encroachment upon the esophagus by enlarged collateral vessels which are typical for the anomaly. Although rare, such a finding can be considered to be additional roentgenologic evidence of coarctation of the aorta.

PICK

CONGESTIVE HEART FAILURE

Wood, J. E., Jr., Ferguson, D. H., and Lowrance, P.: Cation Exchange Resins as an Adjunct in Treatment of Heart Failure. J.A.M.A. **148:** 820 (March 8), 1952.

Resodec has been administered in 50 subjects with and without edema for long and short periods. No serious uncontrollable toxic effects are noted. Hypokalemic effects encountered after the administration of an ammonium cation resin do not appear to occur with the ammonium-potassium cation resin. The chief hazards associated with administration of ammonium-potassium cation resin are the low salt syndrome, azotemia, and mild to moderate transient acidosis. The outstanding contraindication to the use of the resin is impaired renal function. This type of restriction of sodium absorption is useful therapeutically in certain patients with obstinate edema of heart failure, cirrhosis of the liver with ascites and edema, and perhaps edema of the nephrotic syndrome.

KITCHELL

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Rashkoff, I. A., Schaefer, L. E., Magida, M. G., and Levy, H.: Evaluation of Dicumarol Therapy in 287 Cases of Acute Myocardial Infarction. J. Mt. Sinai Hosp. **18:** 350 (March–April), 1952.

One hundred and forty-two cases of acute myocardial infarction admitted to one medical service of a large general hospital were treated with dicumarol; 145 cases of myocardial infarction admitted alternately to the other medical service of the same hospital served as a control series. Both series included only cases who survived more than 24 hours. Other than the employment of dicumarol in the first group, therapy was generally similar in both groups. The two groups were found to be comparable as to age and sex, previous myocardial infarctions, severity of illness, duration of illness

before hospitalization, and the frequency of the use of digitalis. The death rate in the dicumarol group was 13 per cent; in the control series, 27 per cent. The incidence of thromboembolic complications was 14 per cent in the former group and 26 per cent in the latter. The dicumarolized patients showed a marked decrease in the number of pulmonary and cerebral emboli, but phlebitis occurred with nearly equal frequency in the two groups. Subsequent coronary thrombosis occurred in eight of the treated group, and only in five of the control group. In only 4 per cent of the dicumarol-treated cases was death associated with clinically evident thromboembolic complications, in comparison with an incidence of 10 per cent in the control group. The reduction in mortality in the dicumarol-treated group was evident in all the age groups. Eight minor hemorrhagic complications were recorded in the dicumarol group, and one death which may have been due to dicumarol, although there was no apparent hemorrhage.

CORTELL

Morris, J. N., and Heady, J. A.: Coronary Heart Disease in Medical Practitioners. Brit. M. J. **4757:** 503 (March), 1952.

A study was made of clinical coronary heart disease diagnosed among over 6000 male medical practitioners. The average annual incidence of first clinical attacks of coronary heart disease ("coronary thrombosis"—acute myocardial infarction—and angina pectoris) in these medical practitioners during 1947–1950 increased with age, to reach 16.6 per 1,000 at 60 to 64 years.

The coronary death rate in 1947–1950 similarly rose with age to 7.4 per 1,000 at 60 to 64 years.

On current experience, the probability that the individual practitioner member under 45 years of age who has not yet been attacked by it will be attacked by clinical coronary heart disease before he reaches 65 is about one in five, or 20 per cent. The chances that the individual practitioner under 45 years of age will die of it are about one in fourteen, or between 7.1 per cent and 7.5 per cent.

The outlook for life of men first presenting with angina pectoris was very much better than for the others. During the five years from the date of onset, about 11 per cent of them died; their prognosis for life was therefore about the same as in men first presenting with "coronary thrombosis" who had survived the first month, with its 38 per cent mortality.

The incidence of first attacks of coronary heart disease in 1947–1950 was twice as high among the full-time general-practitioner members aged 40 to 64 as in the rest.

Finally, the experience of these medical practitioners was compared with that of a large miscellaneous group of men in the civil services, in the professions, and in industry. The incidence of coronary heart disease in this nonmedical group was well below that of the full-time general practitioners, and resembled that of the other doctors. A comparison with the provisional mortality rates from coronary disease among the males of England and Wales in 1950 gave similar results.

BERNSTEIN

Herndon, R. F., and Smith, H. L.: Unusual Location of Pain in a Patient with Angina Pectoris. Proc. Staff Meet. Mayo Clin. **27:** 121 (March), 1952.

The authors present the case history of a 73 year old male whose symptoms and signs were typical of those of a patient with coronary sclerosis and angina pectoris, except that the pain was solely in the right side of the thorax and related to effort, big meals, and excitement. This condition in their experience is rare, but it is interesting to note that this patient had proved cholelithiasis and never tried nitroglycerine for relief of the chest symptoms.

SIMON

Yater, W. M., Cole, S. L., Sugarman, J. N., Bean, W. B., and Read, C. T.: Cerebral Symptoms in Cardiac Infarction. Lancet **262:** 652 (March), 1952.

Usually the first and foremost symptom of cardiac infarction is pain; but occasionally this is slight or absent, or is rapidly superseded by other symptoms. Notable among these are unconsciousness, convulsions, hemiplegia, or other evidence of local brain injury. In a large series of cases of cardiac infarction in American servicemen under 40 years of age, Yater noted unconsciousness in 11 per cent and convulsions in 4 per cent; and all the patients with convulsions died. In the elderly, cardiac infarction may manifest itself in transient or long-continued unconsciousness and hemiplegia, and the true diagnosis may then be revealed only by necropsy. The neurologic disturbance may be due to ischemia and anoxia from fall in blood pressure, associated with narrowing of the cerebral arteries. Syncope and convulsions may be caused by a slow heart rate due to heart block or even extreme sinus bradycardia, and also by auricular fibrillation and flutter, and the ventricular and auricular tachycardias.

Cerebral symptoms starting days or weeks after cardiac infarction may be due to an embolus from the left ventricle or to arterial disease of the brain.

BERNSTEIN

Master, A. M., and Jaffe, H. L.: Factors in the Onset of Coronary Occlusion and Coronary Insufficiency. J.A.M.A. **148:** 794 (March 8), 1952.

Activities preceding the onset of symptoms in 2,080 attacks of acute coronary occlusion and in

100 episodes of acute coronary insufficiency were studied. These two conditions can be differentiated electrocardiographically in 95 per cent of the cases because coronary occlusion produces through-and-through infarction, and coronary insufficiency causes only subendocardial necrosis. It is felt that coronary insufficiency is at least as common as coronary occlusion. Probably coronary occlusion is a spontaneous event in the course of atherosclerosis, and in the series only 2 per cent of the cases were associated with unusual effort. Occupation, season, and time of day do not influence the incidence. The onset was spontaneous in 56 of 100 attacks of coronary insufficiency. In the remaining 44 the commonest precipitating factors were hemorrhage, pulmonary embolism, effort, tachycardia, operation, excitement, and meals. Angina pectoris almost always is related to effort. Coronary insufficiency is related to effort in about half the cases, and coronary occlusion only rarely and coincidentally. In considering the disability and employability following coronary occlusion, the writers state that in general the outlook for the worker after coronary occlusion is better than it was formerly thought. One half to two thirds of patients return to gainful employment within one year. In coronary insufficiency, the prognosis is even better.

KITCHELL

ELECTROCARDIOGRAPHY

Tobien, H. H. A Simple Method for Determination of the Main Direction of Frontal Vector Loops. Ztschr. Kreislaufforsch. **41:** 171 (March), 1952.

The author presents a table in which the direction of the mean vector in the frontal plane is correlated with the contour of standard and unipolar limb leads. Using this table, it is possible to determine the direction of the vector without measurements of deflections in single leads and without geometric constructions. The principle of the method is similar to that used by Grant and implies the fact that the mean vector is perpendicular to the axis of that lead which shows deflections of equal size in both positive and negative directions. The theoretic basis of the method is discussed and its practical application demonstrated on one example.

A comparative study of 100 normal electrocardiograms revealed that the direction of the mean frontal vector determined by this method was in accordance with the mean electrical axis of QRS constructed by conventional methods, as well as with the type index used by Schlomka. With deviation of the electrical axis to the left the angle between QRS vector and T vector tended to become larger compared with cases with an intermediate axis or right axis deviation.

PICK

Steinberg, M. F., Kroop, I. G., and Grishman, A.: The Value of Intracardiac and Esophageal Leads in the Analysis of Complex Arrhythmias. J. Mt. Sinai Hosp. **18:** 337 (March–April), 1952.

The authors report six cases of arrhythmias where either esophageal or intracardiac leads were useful in elucidating the mechanism involved because of their ability to demonstrate atrial complexes not recorded by the conventional electrocardiograms. The first case was that of a patient with chronic rheumatic mitral and aortic valvular disease, whose conventional electrocardiograms showed periods of apparent sinus arrhythmia or sinus arrest, and occasional premature beats which appeared to be ventricular extrasystoles. Intracardiac leads revealed atrial premature contractions, either blocked or followed by an aberrantly conducted ventricular complex. The failure of the conventional leads to record the atrial complexes had resulted in tracings which resembled either sinus arrest or premature ventricular contractions. The second case was that of a man who, in the course of a routine electrocardiogram, was found to have regular sinus rhythm with frequent ventricular premature contractions and occasional short runs of ventricular tachycardia. Both esophageal leads at atrial levels and intracardiac leads revealed retrograde atrial excitation with suppression of sino-atrial node activity. The same patient was later admitted because of paroxysmal tachycardia.

Esophageal leads showed atrial flutter complexes which were not discernible at all in conventional leads. The third case again demonstrated retrograde atrial complexes and suppression of sino-atrial node activity during short runs of ventricular tachycardia produced by mechanical stimulation of the interventricular septum during cardiac catheterization. These retrograde atrial complexes were not visible in the conventional electrocardiograms.

Two patients with arteriosclerotic and hypertensive heart disease in congestive failure showed regular rhythm without discernible atrial activity in the conventional electrocardiograms. In one, intracardiac leads revealed atrial tachycardia, complete heart block, and idioventricular rhythm; the other case was shown to have atrial flutter by means of esophageal leads. The sixth case was a man who had frequent episodes of palpitations and whose standard electrocardiograms showed an almost regular rhythm with no definite atrial complexes. Esophageal leads and intracardiac leads showed atrial tachycardia with 2:1 ventricular response, which changed to atrial flutter and then fibrillation during the course of recording the intracardiac leads.

CORTELL

Laham, J., and Barbour, D.: The Electrocardiographic Diagnosis of Combined Ventricular Strain. Arq. brasil. cardiol. **5:** 62 (March), 1952.

Notwithstanding the difficulties encountered in the electrocardiographic diagnosis of combined ventricular strain, the authors believe that it is possible to recognize coexistent right and left ventricular hypertrophy when the tracings conform to one of the following patterns:

1. Right axis deviation, with signs of right and left ventricular hypertrophy in precordial leads. The electrical position of the heart is vertical and there is marked clockwise rotation on the longitudinal axis.

2. Evidence of left ventricular hypertrophy in a vertical heart with marked clockwise rotation.

3. Signs of left ventricular hypertrophy with marked left axis deviation, displacement of the transitional zone to the left in precordial leads, marked counterclockwise rotation, and backward displacement of the cardiac apex.

In addition to the three major electrocardiographic patterns, there are certain tracings in which the diagnosis is impossible in the absence of clinical and roentgenologic data. The tracings may be normal but usually show some signs of left ventricular hypertrophy. There is a notable absence of clockwise rotation, and the S wave is persistent in lead V_5. Most cases correspond to mitroaortic valvular heart disease with a prominent aortic lesion.

SCHLESINGER

Zao, Z. Z., and Laranja, F. S.: Hexaxial System with Circles of Polarity: a Simple Method for the Determination of Cardiac Vectors in the Frontal Plane. Arq. brasil. cardiol. **5:** 82 (March), 1952.

A practical method is described for the rapid determination of the approximate direction of any cardiac vector, based on the polarity of the standard and unipolar limb leads.

Six concentric circles are drawn, the innermost representing lead I and the outermost lead V_F. Each circle is divided into a positive and a negative semicircle, of 180 degrees. The center represents the origin of any cardiac vector projected on the frontal plane of the body. The six axes divide each circle into six segments of 30 degrees. There are two transitional zones in each circle, representing changes from positive to negative polarity. Transitional complexes (zero potential) are marked at these points. In order to determine the direction of any given vector, the polarity of the deflection is verified in each of the six successive leads and marked on the positive or negative semicircle corresponding to each lead. The direction of the cardiac vector is obtained by uniting the center to the respective segments of each one of the six concentric circles and reading the number of degrees marked on the outer circle corresponding to lead V_F.

SCHLESINGER

Joos, H. A., Yu, P. N. G., and Katsampes, C. P.: QT_c Interval in the Diagnosis of Rheumatic Fever. Am. J. Dis. Child. **83:** 320 (March), 1952.

In 52 cases of active rheumatic fever, the $Q\text{-}T_c$ interval was significantly prolonged (greater than 0.424 second) in 84 per cent. The $Q\text{-}T_c$ interval was in the doubtful range (0.415 to 0.424 second) in 12 per cent. Four per cent of the cases with rheumatic activity had $Q\text{-}T_c$ values of less than 0.415 second. There were two cases of acute rheumatic pericarditis in which the $Q\text{-}T_c$ intervals were in the low range. As the pericarditis subsided, there was an increase in the Q-T interval. There were no patients with active rheumatic fever who had a $Q\text{-}T_c$ interval shorter than 0.407 second.

In 18 children with quiescent rheumatic fever, the $Q\text{-}T_c$ intervals were significantly prolonged in 12 per cent, doubtful in 19 per cent, and normal in 69 per cent. The consistent prolongation of the $Q\text{-}T_c$ interval in cases of known active disease makes active carditis much more likely in cases in which the disease is clinically quiescent and in cases of suspected active rheumatic fever, if the $Q\text{-}T_c$ interval is significantly lengthened.

In 70 patients with acute infectious disease, 10 per cent showed a prolongation of the $Q\text{-}T_c$ interval. Most of these cases were acute poliomyelitis. Myocarditis is known to occur during acute infections of all types, and the electrocardiographic changes may therefore simulate those of acute rheumatic fever. A prolonged $Q\text{-}T_c$ might be expected to occur in these cases.

The electrocardiogram is here employed to evaluate a physiologic property of the myocardium rather than its anatomic continuity. The authors stress that physiologic measurements are subject to many biologic influences, each of which must be understood in order to make the measurement of value in prediction. The Q-T interval may be shortened by pericarditis, digitalis, and the salicylates. It may be prolonged by apprehension or excitement, exercise, quinidine, hypertension, cardiac decompensation, hypocalcemia, and hypopotassemia. In cardiac arrythmias the Q-T interval may be variable and unpredictable. Therefore, the authors state that the $Q\text{-}T_c$ interval is a sensitive diagnostic aid in detecting active carditis, provided an adequate technique of measurement is employed and all factors which effect the Q-T interval are evaluated.

MARGOLIES

Ross, L. J.: Electrocardiographic Findings in Measles. Am. J. Dis. Child. **83:** 282 (March), 1952.

Seventy-one children with measles who ranged in age from 4 to 14 years were studied. The author did not note symptoms and clinical signs of myocarditis, such as easy fatigability, congestive heart failure, and cardiac insufficiency.

The study of 105 electrocardiographic records of the 71 children revealed the P-R interval increased in 30 per cent, an R′ wave in CF_2 in 28 per cent, and a prolongation of the Q-T interval in 29 per cent. It was not possible to perform serial electrocardiograms to determine the time required for the tracings to return to normal. Cardiac damage has not been believed to follow. Nevertheless, the author suggests that it may be desirable to extend the period of rest after measles, especially for children under 8 years of age in whom a higher incidence of electrocardiographic disturbances was found.

MARGOLIES

Zemplenyi, T.: New Applications of Synchronous Three or Four Lead Registration in Modern Electrocardiography. Acta med. scandinav. **141:** 292 (March), 1952.

An application of the Kayser Weber system of electrocardiographic registration is described. By this system two leads are registered separately by two separate oscillographs, while a third oscillograph automatically registers the difference between the excursions of the second and first leads. The relation between the unipolar limb leads introduced by Wilson and the standard leads is easily studied by this technic, since two of the unipolar limb leads are registered simultaneously while the third oscillograph registers the standard lead derived from them. The author has also used this system to analyze the relation between chest leads C_R, C_L, C_F, and the potential variations of the extremities. He has found that the use of one of the extremities as a point of reference in recording the precordial leads introduces distortions of the S-T segment and biphasic excursions due to asynchronicity. Registration of precordial leads by means of the central terminal method of Wilson is considered the safest technic.

ROSENBAUM

Converse, J. G., Landmesser, C. M., and Garmel, M. H.: Electrocardiographic Changes during Extubation. A Study of Electrocardiographic Patterns during Endotracheal Anesthesia including those seen during Intubation, Endotracheal Suction, and particularly Extubation. Anesthesiology **13:** 163 (March), 1952.

Electrocardiograms were taken on 41 patients immediately prior to induction of anesthesia and during various phases of endotracheal anesthesia. During intubation 20 patients showed electrocardiographic changes—3 abnormal cardiac rhythms and 18 rate changes. During endotracheal suction prior to extubation, 17 patients demonstrated changes—two abnormal cardiac rhythms and 16 rate changes. During extubation 19 showed electrocardiographic changes—5 abnormal rhythms and 17 rate changes.

The authors believe that these studies tend to deny the alleged cardiac dangers of extubation during light planes of anesthesia because the arrhythmias observed were so fleeting in nature and also because these patients had a benign postoperative course. The authors suggest that the relative low incidence of electrocardiographic changes found in this series might be due to the practice of employing 100 per cent oxygen before any endotracheal manipulations. The incidence of electrocardiographic changes during endotracheal manipulations was higher with inhalation agents alone than when intravenous Pentothal was used in conjunction with inhalation anesthetics. Intravenous procaine or the application of topical pantocaine to the larynx did not affect the changes occurring during intubation. Changes were observed more frequently in thoracic and upper abdominal operations. Patients who were classified as being in an abnormal cardiac status preoperatively, for some unknown reason, had less cardiac arrhythmias during endotracheal manipulation than those with normal hearts.

SAGALL

Bush, O. F., Bittenbender, G., and Adriani, J.: Electrocardiographic Changes during Ethyl Chloride and Vinyl Ether Anesthesia in the Dog and Man. Anesthesiology **13:** 197 (March), 1952.

During ethyl chloride anesthesia in dogs, electrocardiograms showed the first effect on the heart to be an inhibition of the conducting mechanism due to vagal stimulation. This occurred 18 to 120 seconds after induction and was noted during plane 1 or 2 of stage III anesthesia. This appeared in all animals not premedicated with atropine. Later in the course of anesthesia (planes 2, 3, or 4 of stage III or stage IV), depressant effects of ethyl chloride on the cardiac tissues occurred. These always followed the vagal inhibition when it occurred and were preceded in most instances by brief periods of excitation shown by tachycardia. As the concentration was increased death resulted from asystole or ventricular fibrillation. Atropine did not protect against the depressant action of the drug.

In man the vagal inhibition was also found in patients anesthetized without the pre-anesthetic use of atropine. The effect could be reversed by the intravenous injection of atropine. Similar studies in man and dog with vinyl ether without pre-anesthetic medication of atropine or morphine failed to show either the vagal inhibition or the depression of cardiac tissues found with ethyl chloride.

The electrocardiographic changes observed during ethyl chloride anesthesia are of serious nature and may indicate a possible cause of sudden death during anesthesia with this agent. In all cases the use of ethyl chloride without atropine is not justified. From the point of view of effect on the heart, vinyl ether appears to be preferable to ethyl chloride as an inhalation anesthetic.

SAGALL

Fisher, K., and Winsor, T.: Contributions of Electrocardiography to Anesthesia for Chest Surgery. Anesthesiology **13:** 147 (March), 1952.

The treatment of cardiac emergencies occurring during anesthesia is under the usual conditions based almost entirely upon the pulse rate, blood pressure, and the clinical appearance of the patient. Since alteration of cardiac function occurs frequently during chest surgery, additional information concerning the cardiac status prior to, during, and after anesthesia is of importance in determining proper therapy.

A study was made of the course of 102 patients who underwent chest surgery. In 52 patients electrocardiograms were taken before, during, or immediately after the chest surgery. It was found that in the latter group the electrocardiograms were a valuable aid in discovering cardiac arrhythmias that were otherwise undetectable and were often serious. The electrocardiogram also provided a means of determining the efficacy of treatment for cardiac abnormalities administered either prophylactically or therapeutically.

Cases are discussed illustrating the detection and treatment of various arrhythmias, the detection of myocardial injury, and the value of prophylactic administration of banthine and digitalis in selected patients. The mortality of the patients anesthetized under electrocardiographic control was zero as compared with 6 per cent in the group in whom electrocardiograms were not taken. The authors believe that this lowered mortality was directly due to better therapy resulting from the additional information afforded by the electrocardiograms.

SAGALL

Mauro, A., Nahum, L. H., Sikand, R. S., and Chernoff, H.: Equipotential Distribution for the Various Instants of the Cardiac Cycle on the Body Surface of the Dog. Am. J. Physiol **168:** 584 (March), 1952.

The authors have studied the fundamental geometric pattern of equipotential lines on the surface of the dog chest. The pattern obtained could not be explained on the basis of a planar or spherical surface doublet distribution. The distribution of lines was similar in man and dog except for the location of maximum positive and negative regions. The "electrical axis" of Einthoven did not agree as to direction with a line joining the maximum positive and negative regions. Manifest potentials from Einthoven's formula were different from those actually observed.

OPPENHEIMER

HYPERTENSION

Stearns, N. S., and Ellis, L. B.: Acute Effects of Intravenous Administration of a Preparation of *Veratrum Viride* in Patients with Severe Forms of Hypertensive Disease. New England J. Med. **246:** 397 (March 13), 1952.

A biologically standardized preparation of alkaloids from *veratrum viride* was given intravenously 36 times to 25 patients with severe or malignant hypertensive vascular disease. The infusions were given at two different rates: a relatively rapid one of 0.88 to 1.0 microgram per kilogram per minute, and a relatively slow rate of 0.6 to 0.68 microgram per kilogram per minute. The onset of vasodepressor effect usually began in 8 to 14 minutes. There was often a continued fall in the blood pressure after the infusion was stopped. The vasodepressor effect lasted from three minutes to 12 hours. Hypotension with symptoms of collapse occurred in one patient but was treated successfully with intravenous neosynephrine. The dose required was quite variable from patient to patient, and it is recommended that it be determined on the basis of the patient's weight and his vasodepressor response during the infusion of the drug. There was no clinical evidence of increased insufficiency of any of the vital organs during the hypotensive response. Symptomatic improvement occurred in 18 trials in 14 patients. Patients with hypertensive encephalopathy showed the most favorable immediate responses, although these were not usually the most persistent. The survival data for the patients studied showed no material alteration in the course of the hypertensive disease except possibly in three patients. The authors conclude that intravenous use of this drug seems to have a place in the treatment of the symptoms of hypertensive crises or encephalopathy.

ROSENBAUM

Skeggs, L. T., Kahn, J. R., and Shumway, N. P.: The Isolation and Assay of Hypertensin from Blood. J. Exper. Med. **95:** 241 (Mar.), 1952.

A method has been described for isolation and assay of hypertensin from the blood of dogs. An ethanol filtrate of blood drawn from the femoral artery is prepared and concentrated by evaporation. The hypertensin is extracted into *n*-butanol from which it is adsorbed into alumina, and subsequently eluted with dilute ethanol. The eluate is then evaporated to dryness, dissolved in water, and assayed by intravenous injection into rats.

BERNSTEIN

Campbell, A. J. M., Graham, J. G., and Maxwell, R. D. H.: Treatment of Hypertension by Oral Methonium Compounds. British M. J. **4752:** 251 (Feb.), 1952.

Hexamethonium, pentamethonium and hexa-methylene bisdimethylethyl ammonium ("M. & B. 1863") in bromide, chloride, iodide, and tartrate salts were used for up to two years in the treatment of an unselected group of 35 patients with hypertension and severe symptoms and signs. These compounds

were used orally with variable results upon the blood pressure, but in 23 of the 35 patients there was a good symptomatic improvement with regression of the signs.

Hexamethonium also produced a symptomatic improvement in five patients with severe chronic nephritis, and in two with malignant hypertension.

BERNSTEIN

Shapiro, A. P., and Ferris, E. B.: The Effects of Intravenously Administered Veratrum Viride in Hypertensive and Normotensive Subjects. Ann. Int. Med. **36:** 792 (March), 1952.

The effect of intravenous administration of veratrum viride on blood pressure and pulse rate was studied in 38 hypertensive and 10 normotensive subjects. The results demonstrated a similar depressor response to a fixed dose in both groups. Considerable variability of this response was exhibited within each group. The individual degree of response in the hypertensive patients could be correlated only with the initial diastolic pressure, in that patients with higher levels showed a significantly smaller percentile fall. Symptoms of nausea and vomiting were present in one third of the patients. They were unrelated to the percentile fall of blood pressure and were not diminished by simultaneous administration of atropine sulfate. However, atropine did prevent bradycardia without significantly affecting the depressor response. Repeated interval injections of veratrum viride revealed no evidence of the development of tolerance in the blood pressure response. In addition, studies with doses of increasing size demonstrated a "leveling off" of the dose-effect curve, with the eventual appearance of nausea and vomiting as the limiting factor to further increase. The studies bear out the ability of veratrum viride consistently to produce a fall in blood pressure, but emphasize the difficulty in determining individual responsiveness to the drug.

WENDKOS

Shapiro, A. P., Brust, A. A., and Ferris, E. B.: A Comparative Study of the Effects of Veratrum Viride and Tetraethylammonium Chloride in Hypertension. Ann. Int. Med. **36:** 807 (March), 1952.

The effects of intravenous administration of veratrum viride and tetraethylammonium chloride were compared in 15 patients with hypertension. In contrast to toxemia of pregnancy, where the results of the two drugs are diametrically opposed (tetraethylammonium chloride having little or no effect and veratrum viride producing a marked fall in blood pressure), these 15 patients showed a similar blood pressure fall to each drug when they were given on the same day. The results support the concept that the vasodilatation produced by veratrum viride is not specific in terms of the various mechanisms interrelated in the maintenance of the elevated blood pressure, but depends on the degree or severity of peripheral resistance which is present.

WENDKOS

PATHOLOGIC PHYSIOLOGY

Krasemann, E. O.: Three Cases with Marked Pressure Elevation of the Pulmonary Circulation for Particular Reasons. Ztschr. Kreislaufforsch. **41:** 210 (March), 1952.

The author reports three unusual cases in which autopsy revealed rare cardiac anomalies associated with an increase of pressure in the pulmonary circulation. In the first case, diagnosed clinically as aortic regurgitation, an inflammatory process of the aortic wall with perforation of the latter 2 cm. above the semilunar valves resulted in an aortopulmonic fistula and in secondary sclerosis of the pulmonary vascular tree.

In the second case an aortic aneurysm of syphilitic etiology encroached upon the pulmonary artery with subsequent stenosis of this vessel. The third case, with the clinical symptomatology of mitral disease, showed at post mortem a large organized thrombus (pseudomyxoma) in the left atrium, attached to an old endocarditic scar which partially occluded the mitral ostium. In all three cases pulmonary hypertension was evidenced by marked right ventricular hypertrophy.

PICK

Reissmann, K. R., Burkhart, W. L., and Hoelscher, B.: Blood Destruction in the Polycythemia Induced by Hypoxia. Blood **7:** 337 (March), 1952.

The authors studied the hemoglobin catabolism during the development and during the disappearance of polycythemia induced by hypoxia before, during, and after prolonged periods of exposure to 20,000 feet simulated altitude. This was studied by measuring the total circulating hemoglobin and the daily bile pigment excretion in bile-fistula dogs. They found that the increased erythropoiesis during the first weeks of altitude exposure was accompanied by a significant increase in bile pigment output. The life span of the red cells during altitude exposure was found to be about 115 days. This was essentially the same as that observed in animals at ground level. The blood returned to ground level. This was achieved by the combined effect of a depressed erythropoiesis and of an increased blood destruction. The authors conclude that the increase in red cell destruction observed under these conditions demonstrates the existence of a mechanism of blood destruction by which the organism is able to destroy normal blood cells before their life span is exhausted. They found, however, that increased red cell destruction accounted for only 21 to 39 per cent of the

hemoglobin which disappeared from circulation after return to ground level. The chief factor in the normalization of altitude polycythemia was the temporary depression of erythropoiesis which they estimated to amount to 30 to 40 per cent of the normal cell production in the six week period after the discontinuation of the altitude exposure.

BEIZER

Taylor, H. L., and Tiede, K.: A Comparison of the Estimation of the Basal Cardiac Output from a Linear Formula and the "Cardiac Index." J. Clin. Investigation **31:** 209 (Feb.), 1952.

The cardiac index assumes that the cardiac out put normally is directly proportional to the surface area of the body. This report examines the validity of the cardiac index as a standard, particularly in its usefulness in predicting the cardiac output. Forty-eight healthy male students are studied. Cardiac outputs are estimated by the acetylene method and by the low-frequency, critically damped ballistocardiograph. In addition, the authors reviewed the data of Tanner using the high-frequency ballistocardiograph, acetylene method and ethyl iodide method.

It is found that the high-frequency ballistocardiograph gives estimates of cardiac output which are not related to surface area and body size, and it is an unsatisfactory method in this regard. Similar findings are noted with the ethyl iodide procedure. On the other hand, the low-frequency critically damped ballistocardiograph, the acetylene method, direct Fick procedure, all distinguish between large and small persons more satisfactorily. These three methods give cardiac outputs, which are related to surface area in such a way that the use of the cardiac index adds only a small (less than 3.6 per cent) additional variance over that found by the more efficient least-squares method. Even in the best situation, the variability attributable to differences in surface area accounts for only 20 per cent of the total variability observed. The cardiac index is a standard which, although somewhat less efficient than the regression line, may be used as a standard to predict cardiac outputs of individuals. It should always be accompanied by precise age specifications, since the cardiac index varies with age. Although the error involved in predicting cardiac output of an individual is small compared with the total variability in cardiac output, the problem of comparing groups is quite different, since small differences can be significant where large groups are involved.

WAIFE

Mokotoff, R., Ross, G., and Leiter, L.: The Electrolyte Content of Skeletal Muscle in Congestive Heart Failure; A Comparison of Results with Inulin and Chloride as Reference Standards for Extracellular Water. J. Clin. Investigation **31:** 291 (March), 1952.

In estimating electrolyte shifts between the intracellular and extracellular fluid compartments, or in calculating intracellular electrolyte concentrations from tissue analysis, certain assumptions dealing with the distribution of chloride, and initial or final volume of extracellular water are necessary. Since the volume of inulin distribution is smaller than that of chloride or other electrolytes, it has been suggested that inulin is confined to the extracellular compartment. In an effort to obtain a more precise measurement of the extracellular fluid of muscle, inulin was infused into experimental subjects until uniform distribution had been achieved. Muscle was obtained by biopsy and analyzed for inulin and electrolyte content.

Seven patients were studied, four noncardiacs and three cardiacs with congestive failure after prolonged inulin infusion. In three additional cardiacs, biopsies were taken without prior inulin infusion. Based on the values obtained if one excepts the "chloride space" or a "corrected chloride space" as the reference standard for extracellular water, it can be shown that the cardiac with heart failure has a loss of intracellular potassium and a gain of intracellular sodium. On the other hand, with inulin as a standard, there is no change from the normal in the intracellular electrolyte composition in heart failure. From the present data one cannot select the true reference standard for measuring extracellular water.

WAIFE

Penneys, R.: Studies with the Millikan Oximeter at the Bedside of Patients with Cardiac and Pulmonary Disease. Bull. Johns Hopkins Hosp. **90:** 192 (March), 1952.

Twenty-seven patients with cardiac and pulmonary disease were studied at the bedside with the use of the Millikan automatically compensated type of oximeter. The Millikan oximeter is an instrument which measures changes of the blood arterial oxygen saturation in the intact human ear.

Hypoxemia was detected when, with the administration of pure oxygen by demand valve, the arterial oxygen saturation increased to greater than the normal of six per cent. In the same patient, the severity of hypoxemia paralleled the severity of the disease. The author suggests the saturation rise with oxygen as an objective test of the clinical course of such patients.

Polycythemia vera may be differentiated from secondary polycythemia by measuring the arterial saturation rise with oxygen inhalation. Primary polycythemia produces a normal rise, since the arterial saturation of the blood while breathing air is normal. Secondary polycythemia associated with pulmonary disease will give a saturation rise greater than 6 per

cent if the blood is abnormally unsaturated while breathing air and becomes fully saturated with oxygen inhalation.

The diagnosis of carbon monoxide intoxication may be strongly questioned if hypoxemia is detected on the oximeter.

The use of the demand valve to administer oxygen is important, since hypoxemic patients require high concentrations of oxygen to completely saturate their blood.

It was found that for the same severity of disease, "pulmono-cardiac" patients were more unsaturated than "pulmonary," and "pulmonary" patients were more unsaturated than "cardiac" patients.

The author has found the Millikan oximeter a simple and useful instrument for the detection, treatment, and understanding of hypoxemia at the bedside of patients with cardiac and pulmonary disease.

MARGOLIES

McGirr, E. M.: The Rate of Removal of Radioactive Sodium Following Its Injection into Muscle and Skin. Clin. Sc. **11:** 91 (March), 1952.

Clearance rates of sodium^{24} from muscle and skin were determined in normal subjects as well as in persons with intermittent claudication. The rates show considerable variation among normal subjects, the clearance always being exponential. In general, clearance rates are affected by changes in blood flow, though not in a strictly proportional manner. Temperature changes affect clearance from the skin much more than from the muscle. The method is capable of revealing marked changes in local circulation. Its diagnostic application to cases of intermittent claudication with readings taken at rest has not been helpful. However, it will be necessary to examine the results of studies during exercise before the method can be evaluated as a diagnostic tool.

ENSELBERG

Lequime, J., Denolin, H., and Vernegry, A.: The Circulation in the Course of Paget's Disease. Acta Cardiol. **7:** 319 (Fasc. 3), 1952.

Data of the literature indicate that Paget's disease is associated with marked alterations of the circulation (increase of cardiac output and diminished A-V oxygen saturation) which is the result of arteriovenous shunts in vascular communications in the diseased bones.

The authors studied the cardiodynamics in a 63 year old patient with typical roentgenologic findings of disseminated Paget's disease. Cardiac output and peripheral arterial resistance, calculated on the basis of catheterization data, were normal; however, the oxygen content of the venous blood was much lower in the upper extremities than in the legs, which showed the most pronounced osseous changes. It is concluded that, in the studied case, arteriovenous shunts were present in the lower extremities but of insufficient magnitude to increase cardiac output and to alter significantly the general circulation.

PICK

Papaemanuel, S., Papanicolis, I., and Lazaron, P.: Chronic Cor Pulmonale in Tuberculous Patients. Arch mal. coeur **45:** 259 (March), 1952.

Among 100 cases with chronic pulmonary tuberculosis, 10 per cent had electrocardiographic changes suggesting chronic cor pulmonale. Ten cases were submitted to cardiac catheterization. In eight instances moderate elevation of the pulmonary arterial pressure was found, while the electrocardiogram showed marked right axis shift but no evidence of right ventricular hypertrophy. In two cases in whom the electrocardiogram indicated hypertrophy of both right auricle and ventricle, the right ventricular pressure was markedly elevated. The authors feel that in cases with extensive pulmonary lesions and electrocardiographic signs of right ventricular hypertrophy, cardiac catheterization and determination of intraventricular pressures are necessary before any active therapy is attempted, in order to avoid precipitation of right ventricular failure in the course of the planned therapeutic procedures.

PICK

Haley, T. J., Riley, R. F., Williams, I., and Andem, M. R.: Presence and Identity of Vasotropic Substances in Blood of Rats Subjected to Acute Whole Body Roentgen Ray Irradiation. Am. J. Physiol. **168:** 628 (March), 1952.

There was no apparent direct effect of irradiation on the mammalian capillary bed. During the first week after exposure, a vasodepressor substance which produced profound peripheral vascular paralysis as does Ferritin, appeared in the circulation. In the second week, a vasoexcitor material appeared. The vasodepressor material was shown to be VDM as in irreversible shock. It is pointed out that the depressor material appears first and the excitor material (VEM) later, which is a different sequence than in shock.

OPPENHEIMER

Frieden, J., Rice, L., Elisberg, E. I., Eisenstein, B., and Katz, L. N.: Effects of Chronic Peripheral Venous Congestion on Renal Sodium Excretion. Am. J. Physiol. **168:** 650 (March), 1952.

The aim of the present study is to determine whether or not chronic venous congestion in any specific circulatory bed is of predominant importance in causing alterations in renal handling of sodium. Ligation, partial or complete, of large veins was used to produce long-standing elevations of venous pressure in dogs. Sodium excretion rate was decreased when peripheral venous pressure became elevated. Glomerular filtration rate and renal plasma flow were unchanged. Establishment of collaterals, which permitted a fall in venous pressure, was accompanied

by an increase in sodium excretion rate. The authors are of the opinion that peripheral venous pressure elevations are important in sodium retention by virtue of increased tubular reabsorption, even though the intermediary mechanism cannot be described.

OPPENHEIMER

Burdette, W. J.: Oxygen Consumption of Cardiac Muscle During Shock. Am. J. Physiol. **168:** 575 (March), 1952.

The authors produced shock by bleeding and also by release of previously applied tourniquests. Serum amino acid levels and appearance of the rats used in these experiments were used as indices of production of shock. Both methods of induction of shock produced equal effects on oxygen use of heart muscle. Oxygen uptake of muscle slices was greater from animals very soon after treatment than from animals without treatment. A depression and secondary rise in oxygen use followed.

OPPENHEIMER

PATHOLOGY

Benchimol, A. B., and Dias Carneiro, R.: Diphtheritic Myocarditis. Arq. brasil. med. **42:** 85 (March–April), 1952.

Following a review of the present concept of diphtheritic myocarditis, the authors report three cases of this condition of which two had autopsy confirmation. In the first patient, a bacteriologic confirmation was not obtained and the diagnosis was based upon the presence of peripheral neuritis appearing some time after a throat infection. Diphtheritic myocarditis was thought to be the cause of longstanding heart failure which responded to cardiotonic medication. This patient was examined one year later and showed a definite increase in heart size which was interpreted as due to irreversible myocardial changes caused by diphtheria. The second case had complete laboratory confirmation, and showed a complete AV heart block in the first week of the disease. Death occurred shortly thereafter following a period of convulsions and loss of consciousness. Autopsy studies confirmed the clinical diagnosis. In the third patient the diagnosis was proved bacteriologically and confirmed at autopsy. Since this case was seen only twelve hours before death, the unfavorable course was probably due to the absence of early and adequate specific therapy.

SCHLESINGER

Murphy, G. E.: Evidence that Aschoff Bodies of Rheumatic Myocarditis Develop from Injured Myofibers. J. Exper. Med. **95:** 319 (March), 1952.

Comparative studies on the histopathogenesis of experimentally induced lesions of myocardial Aschoff body type in rabbits, and of many myocardial Aschoff bodies from several active rheumatic fever patients, have revealed the following: Almost invariably these experimental lesions, and very frequently the myocardial Aschoff bodies studied in their early stages, have been shown to originate in and evolve from lesions of heart muscle fibers. The mono-, multi-, and non-nucleated cell masses, most characteristic of myocardial disease of the rheumatic type, appear to be damaged muscle fibers, their fragments, and syncytial cell masses of probable muscular origin that proliferate from beneath the sarcolemma and in the tracks of damaged muscle fibers in reaction to that damage.

The most distinguishing histologic feature of the myocardial Aschoff bodies in rheumatic heart disease is the peculiar lesions of muscle fibers. Therefore, it is proposed that they be designated as "myofiber Aschoff bodies" in order to indicate their origin more accurately. The results of these investigations contrast with the widely accepted theory that all myocardial Aschoff bodies originate as injured interstitial collagen and that, as they evolve, they consist of damaged interstitial collagen intermingled with cells of nonmyogenic derivation that proliferated in response to that collagen injury.

BERNSTEIN

Williams, A. W.: Primary Amyloidosis with Renal and Myocardial Failure. J. Clin. Path. **5:** 54 (Feb.), 1952.

A case is described of primary systemic amyloidosis in a woman of 49. The illness lasted two years and was accompanied by progressive renal and myocardial failure. The amyloid was mainly of cardiovascular distribution. Most arteries affected by amyloid showed deposits throughout their walls, but in some arteries the amyloid was confined almost entirely to the media.

Reference is made to the four other cases of primary systemic amyloidosis with renal failure reported in the medical literature.

BERNSTEIN

Symmers, W. St. C.: Necrotizing Pulmonary Arteriopathy Associated with Pulmonary Hypertension. J. Clin. Path. **5:** 36 (Feb.), 1952.

Two cases are described in which there was a necrotizing arteriopathy limited to the pulmonary vasculature. Essential (primary) pulmonary hypertension was present in one case, and pulmonary hypertension secondary to mitral stenosis in the other. The lesions in the small blood vessels in each case were of three kinds: (1) arteriolosclerosis, comparable to hypertensive systemic arteriolosclerosis; (2) fibrinoid necrosis of the media of small arteries and arterioles, comparable to the arteriolonecrosis associated with malignant systemic hypertension; and (3) arteritis and arteriolitis, reproducing the histologic features seen in polyarteritis nodosa. It is suggested that necrotizing arteriopathy limited to the pulmonary vasculature and occurring in associa-

tion with pulmonary hypertension is a result of the hypertension and not its cause.

BERNSTEIN

Gordin, R.: An Unusual Case of Combined Rupture of Heart and Aorta. Acta med. scandinav. **141:** 380 (March), 1952.

The onset of pain and clinical illness in a 55 year old woman suggested an acute myocardial infarction. Postmortem examination disclosed a tear in the wall of the right ventricle, 4 mm. in diameter and immediately below the semilunar valves. Blood had extended by extravasation from this tear to the root of the aorta which was then dissected into two layers from its origin down to the level of the renal arteries. The aortic intima was undamaged. The dissection communicated with the pericardial cavity through an opening in the outer wall of the aorta at its root. Massive hemopericardium had occurred. The rupture of the right ventricle was felt to occur at a zone of myofibrosis, and the extension into the wall of the aorta was considered to have followed one of the vasa vasorum.

ROSENBAUM

Rose, I.: Tuberculosis of the Myocardium. Am. Rev. Tuberc. **65:** 332 (March), 1952.

A case is presented of myocardial tuberculosis showing varying types of heart block pointing to involvement of the conduction apparatus of the heart. At necropsy the heart weighed 280 Gm. All chambers were slightly dilated and those of the right heart markedly so. Beneath the epicardium and involving the myocardium and interventricular septum were multiple clusters and patches of rounded, light tan, moderately firm nodules. Histologic sections of the heart showed tuberculous myocarditis with diffuse degeneration of the myocardium and focal caseous tuberculosis. Although no active pulmonary tuberculosis was demonstrated, active tuberculosis was present in the pelvic organs. Myocardial tuberculosis should be considered in a patient who has a primary focus of tuberculosis, and if there are cardiovascular signs present.

BERNSTEIN

PHARMACOLOGY

Burnett, J. B., and Gundersen, S. M.: The Effect of Volatile 1-Cyclohexyl-2-Methylaminopropane ("Benzedrex" Inhaler) on Patients with Coronary Arteriosclerosis. New England J. Med. **246:** 449 (March 20), 1952.

This study was concerned with 1-cyclohexyl-2-methylaminopropane in a volatile form in an inhaler ("Benzedrex"). It differs from amphetamine in that it is a cyclohexylalkylamine rather than a phenylalkylamine. This drug has been found to have less vasopressor activity and to be less stimulating to the central nervous system than amphetamine. Twenty patients with definite coronary arteriosclerosis were tested with excessive doses of this new drug by inhalation. The tests were controlled with inhalers in which no active amine was present. In no patient was there any significant change in the pulse or blood pressure, nor was angina pectoris precipitated. Furthermore electrocardiograms showed no significant changes. In two patients transient ventricular premature beats appeared.

ROSENBAUM

Myers, T. M., and Hamburger, M.: Tuberculous Pericarditis. Its Treatment with Streptomycin and Some Observations on the Natural History of the Disease. Am. J. Med. **12:** 302 (March), 1952.

Three patients with primary tuberculous pericarditis received 1 mg. of streptomycin intramuscularly daily for 90 to 112 days. These patients are still entirely well and lead normal lives 28 months after the cessation of fever. Five of nine patients with similar conditions untreated with streptomycin died within a few months of cardiac failure or miliary spread of the tuberculosis. Although spontaneous healing of the pericarditis occurred in the remaining four untreated patients, tuberculosis appeared elsewhere in the body after an average asymptomatic period of 16.5 months. The authors conclude that tuberculosis of the pericardium may heal spontaneously, but the administration of streptomycin improves the prognosis, although the long-term results cannot be properly evaluated at this time. Death in patients with untreated tuberculosis of the pericardium is perhaps more often due to dissemination of the tuberculous infection than to pericardial involvement, per se.

HARRIS

Schlesinger, P., and Santos, E. M.: Hypersensitivity to the Mercurial Diuretics. Arq. brasil. med. **42:** 105 (March–April), 1952.

Following a brief review of the various types of reactions due to the mercurial diuretics, the allergic manifestations produced by these drugs are emphasized and discussed as to their possible mechanisms.

A case is reported of hypersensitivity to the mercurial diuretics in a patient with hypertensive heart disease who presented a cutaneous reaction following the intravenous administration of this drug. Notwithstanding a change in the mercurial diuretic employed and in the route of administration, as well as the prophylactic use of an antihistamine preparation, a similar allergic reaction occurred several months later. Skin tests with the patch, scratch-patch, and intradermal methods were all positive and confirmed the allergic nature of the erythematous cutaneous reaction.

SCHLESINGER

Paraco, E.: The Cardiovascular Effects and Therapeutic Value of Strophanthidin Benzoate. Arq. brasil cardiol. **5:** 1 (March), 1952.

A study is presented on the cardiovascular effects of strophanthidin-3-benzoate, a substance which maintains the digitaloid activity of the heterosides obtained from Strophanthus kombé. Under experimental conditions the action of this drug seems to be more uniform than that of digitoxin. The quantitative effects of both substances were essentially similar as judged by the respiratory rate, arterial blood pressure, circulation time, and ventricular gradient. The latter effect confirms the direct action of the drug on the cardiac myofibril. In addition to the hemodynamic changes which occur, there is definite improvement of signs and symptoms of heart failure. The drug is completely absorbed when administered by the oral route, although nausea and vomiting are somewhat more frequent as compared to digitoxin. The maximal effect occurs more promptly than that of digitoxin and also declines more rapidly. This type of action is particularly suited for the treatment of severe cases of heart failure. The simultaneous administration of digitalis is indicated in order to obtain the immediate effect of Strophanthus and the delayed action of digitalis. The drug is particularly useful in cases of acute left ventricular insufficiency, and in paroxysmal auricular flutter and fibrillation. The determination of the ventricular gradient, rather than a purely morphologic examination of the T wave of the electrocardiogram, is the most rational method used to measure the effects of this drug.

SCHLESINGER

Moyer, J. H., Miller, S. I., Pashnek, A. B., and Bowman, R.: The Effect of Theophylline with Ethylenediamine (Aminophylline) on Cerebral Hemodynamics in the Presence of Cardiac Failure with and without Cheyne-Stokes Respiration. J. Clin. Investigation **31:** 267 (March), 1952.

Cerebral blood flow studies were performed on 16 patients with cardiac failure, four of whom had Cheyne-Stokes respiration. It was found that aminophylline increased the cerebrovascular resistance in patients with cardiac failure, resulting in a decrease in cerebral blood flow. Changes in arterial carbon dioxide and jugular carbon dioxide indicated that the depression of cerebral blood flow was not a reflection of decrease of carbon dioxide in the brain, but more likely a direct effect of aminophylline on cerebral vessels. The cerebral oxygen consumption decreased under aminophylline. No significant difference was found in the over-all hemodynamic effects in patients with cardiac failure manifesting Cheyne-Stokes respiration.

The effects of this drug are probably due to a stimulating effect on the respiratory center, either directly or indirectly secondary to a depressed cerebral circulation.

WAIFE

Nathanson, M. H., and Miller, H.: Clinical Observations on a New Epinephrine-like Compound, Methoxamine. Am. J. M. Sc. **223:** 270 (March), 1952.

Methoxamine is a sympathomimetic compound which has been recommended for the prevention of the drop in blood pressure that is associated with spinal anesthesia. Its primary advantage is the ability to maintain a pressor effect without affecting the rhythmic function of the heart. Following the intravenous administration of 5 to 10 mg. of Methoxamine, there was a definite slowing of the heart rate which could be abolished or prevented by atropinization. This cardiac inhibition was ascribed to the rise in blood pressure which activates the vagal reflexes with afferent stimulation from the carotid sinuses and aortic arch. This vagal response may be useful in the treatment of supraventricular tachycardia. The drug did not prevent cardiac standstill induced by carotid sinus stimulation. In patients with complete heart block, Methoxamine did not increase the ventricular rate in contrast to epinephrine which invariably caused a sustained rise in ventricular rate. Similar studies on phenylephrine (Neosynephrine) show that this agent frequently has a myocardial stimulating effect.

The authors conclude that Methoxamine is of advantage in the treatment of hypotensive states because the pressor effect is maintained in the absence of any cardiac stimulating action.

SHUMAN

Fox, C., Winfield, J., Slobody, L., Swindler, C., and Lattimer, J.,: Electrolyte Solution Approximating Plasma Concentrations. J. A. M. A. **148:** 827 (March 8), 1952.

A physiologic electrolyte replacement solution which contains sodium, calcium, magnesium, and chloride ions in the normal plasma concentrations is described. Its potassium concentration of 10 mEq. per liter is twice the normal plasma value; likewise, bicarbonate is provided in twice its plasma concentration in the form of rapidly metabolizable precursors, acetate and citrate. The rationale for the use of this solution is presented. In managing the electrolyte and fluid therapy of surgical, pediatric, orthopedic, and urologic patients who lose intracellular potassium after extensive operative procedures or disease, substitution of this solution for 0.9 per cent sodium chloride solution or other solutions has restored acid base balance and prevented the occurrence of hypopotassemia. The available data, both experimental and clinical, indicate that this solution prevents postoperative hypopotassemia without danger of toxicity, corrects moderate acido-

sis without inducing alkalosis, replaces the electrolytes in extracellular fluid, and induces copious secretion of urine and salt. There is now much evidence that 0.9 per cent sodium chloride solution is not the best solution for replacement or supportive therapy, and it is felt that trial of the new solution should be carried out.

KITCHELL

Dogliotti, A. M.: Clinical Use of the Artificial Circulation with a Note on Intra-arterial Transfusion. Bull. Johns Hopkins Hosp. **90:** 131 (Feb.), 1952.

The author describes a technic of intra-arterial blood transfusion through the common carotid artery. The injection of the blood is directed toward the brain. The contention is that it is of greater importance in an emergency to maintain and restore an adequate blood flow to the cerebral centers than to the heart. This is based on the idea that irreversible changes occur in the cerebral centers much before they occur in the heart.

The author's apparatus for sustaining circulatory and respiratory function is also described. The primary function of this apparatus is to complement the activity of the heart and lungs during periods of cardiorespiratory failure. This apparatus has two independent pumps: one sucks the blood from the vein while the other injects it into an artery. The blood removed from the vein is heparinized and oxygenated. The oxygenator consists of a large porcelain filter over which a thin film of blood is passed and brought into contact with finely dispersed gaseous oxygen. The excess carbon dioxide is exhausted by vacuum extraction. The oxygenated blood is pumped back into one of the patient's systemic arteries.

This apparatus was used successfully in a patient undergoing surgery for the removal of a mediastinal tumor. X-ray examination revealed a tumor occupying over half of the upper right thorax and mediastinum. As soon as the pleura was opened, the patient became cyanotic, and engorgement of the cervical veins was evident. The blood pressure could not be obtained. The failing cardiac function was though to be due to compression of the superior vena cava and right auricle by the tumor. The mechanical apparatus was then used. A plastic cannula was inserted into the superior vena cava via the right axillary vein. Another cannula was passed toward the aorta through the right axillary artery. The cannulae were attached to the pump oxygenator. After a few minutes of artificial circulation at 1 L. per minute, the patient's condition improved and surgery could be continued. The tumor was completely removed. The artificial circulation was maintained for 20 minutes. The patient made an uneventful convalescence.

To the author's knowledge, this was the first reported case in which an artificial extracardiac circulation has been successfully used in man.

MARGOLIES

Jourdan, F., and Heyrand, J.: Influence of Acetylcholine and Adrenaline upon Nodal Rhythm. Compt. Rend. Soc. Biol. **145:** 1184 (April), 1951.

Permanent nodal rhythm was produced in rabbits by extirpation of the sinus node, and the effect of acetylcholine, injected intravenously in a dose of 0.25 mg., was studied in electrocardiograms. Compared with the known effects of the drug upon sinus rhythm, the negative chronotrope effect of the drug was more pronounced, leading to marked bradycardia, and in some instances to temporary cardiac arrest of four to seven seconds. A negative chronotrope effect (P–R prolongation) was not observed. The P waves showed modifications in contour of variable degree and in one instance auricular fibrillation set in. The effect of adrenaline, in animals with intact as well as with sectioned vagi, did not differ from that seen usually in animals with sinus rhythm. The demonstration of marked sensitivity of experimental nodal rhythm to pharmacologic vagotropic agents is in accord with results of previous experiments, in which direct vagal stimulation was used.

PICK

King, B. D., Sokoloff, L., and Wechsler, R. L.: The Effects of l-Epinephrine and l-Nor-epinephrine upon Cerebral Circulation and Metabolism in Man. J. Clin. Investigation **31:** 273 (March), 1952.

Cerebral hemodynamics were studied in subjects with apparently normal cardiovascular systems by the continuous intravenous infusions of synthetic l-epinephrine and l-norepinephrine. Epinephrine produced an increase in mean arterial blood pressure and cerebral blood flow without a significant change in cerebral vascular resistance. The cerebral oxygen consumption was significantly increased. On the other hand, norepinephrine produced a marked increase in cerebral vascular resistance and a decrease in blood flow, despite a substantial increase in mean arterial pressure. The oxygen consumption of the brain was not significantly altered.

It is possible that under conditions of maximal vasoconstriction, norepinephrine might increase cerebral vascular resistance out of proportion to the increase in profusion pressure so that cerebral blood flow might actually decrease. These and related drugs should be evaluated not only by their pressor effects but also by blood flow measurements through vital organs in normotensive and hypotensive states.

WAIFE

Kappert, A., Skoglund, C., Bergholtz, A., and Nylin, G.: The Effect of Hydergine (CCK) on Reflex Vasoconstriction and Reflex Blood Pressure Stimulation. Acta med. scandinav. **141:** 440 (March), 1952.

Hydergine (CCK) is a preparation of the hydrogenated alkaloids of ergot, dihydroergocornine, dihydroergocristine and dihydroergokryptine, in equal amounts. These drugs are said to depress the central

tonus of the vessels and possess a peripheral adrenosympathecolytic action, thus resulting in vasodilatation and a fall in blood pressure. The heart rate is slowed by a central effect, and baroceptive reflexes may be blocked and reflex vasoconstriction inhibited when the blood pressure falls suddenly. This study was concerned primarily with the inhibition of reflexly provoked circulatory reactions by means of Hydergine.

It was found that the pressor reaction from the Valsalva maneuver or the cold pressor test, and the peripheral reflex vasoconstriction resulting from indirect cold stimulation or smoking are inhibited or completely blocked by Hydergine. These effects are believed to result from diminution of the vascular tonus and by blockage of the vessels against adrenosympathetic impulses. The effect upon reflexly induced vasoconstriction was found to be more pronounced after intra-arterial administration of the drug than after subcutaneous injection. The reflexly induced increase in blood pressure and the vasoconstriction were more striking in patients with instability of the nervous system and essential hypertension than in normal persons, and the inhibitory effects of Hydergine on these circulatory reactions were more marked when the reflex processes were more pronounced. The authors have given some consideration to the therapeutic application of this drug in cases of hypertension and peripheral vascular disease.

ROSENBAUM

Groen, J., Willebrands, A. F., Kamminga, C. E., Van Schothorst, H. K., and Godfried, E. G.: Effects of Glucose Administration on the Potassium and Inorganic Phosphate Content of the Blood Serum and the Electrocardiogram in Normal Individuals and in Non-diabetic Patients. Acta med. scandinav. **141:** 352 (March), 1952.

This study was undertaken to determine whether endogenous insulin has a potassium-decreasing effect. This was attempted by parenteral administration of glucose to produce a hyperglycemia to form a stimulus to the pancreas, and a follow-up observation to detect hypokalemia at some stage thereafter. Normal and nondiabetic subjects were studied.

During the investigation the test subjects were placed on a low potassium diet. As a rule 100 to 150 Gm. of glucose was introduced over a period of 2 to 3 hours. It was found that administration of glucose either intravenously or orally was followed by a fall in serum potassium in nearly all cases, reaching its lowest point in six to nine hours. A similar fall occurred in the inorganic phosphate although this component returned to a normal level more quickly. Electrocardiographic changes similar to those occurring after large doses of insulin appeared after glucose administration to both normal and nondiabetic patients, but changes typical of hypokalemia developed only when the serum potassium fell to levels of 3.6 mEq. per liter or lower. Such levels appeared only after large doses of glucose administered over long periods of time.

The authors conclude that these decreases in serum potassium and inorganic phosphate are physiologic phenomena occurring regularly when glucose is assimilated by muscle cells under the influence of insulin.

ROSENBAUM

Cloetens, W.: Effect of Procaine Amide on Alternation of Contractility. Acta cardiol. **7:** 347 (Fasc. 3), 1952.

In two cases with mechanical pulsus alternans, intravenous injection of 100 mg. of procaine amide (Pronestyl) was followed instantaneously by a drop of blood pressure, by a decrease of the amplitude of arterial oscillations, and by disappearance of the pulsus alternans. These observations are interpreted in the light of known effects of the drug upon the circulation. Pronestyl apparently slows the speed of ventricular activation to such a degree that all contractile elements, including those with pathologic alterations, have sufficient time to recover from their nonexcitable state between two successive contractions.

PICK

OTHER SUBJECTS

Ellestad, M. H., and Reed, J.: Circulating Eosinophils in Cardiovascular Stress. Ann. Int. Med. **36:** 551 (Feb.), 1952.

Serial eosinophil counts were done in 17 patients with through-and-through myocardial infarction; in 13 patients with subendocardial infarction; in four cases with acute congestive heart failure; and in nine cases with a history suggestive of myocardial infarction associated with inconclusive electrocardiographic findings. In the 17 patients with through-and-through myocardial infarction, there was a drop in the eosinophil count to 20 or below for from two to six days, and all but one were at 20 or below on the second day. About the fifth day, came a sharp rise with a levelling off somewhat below this peak. In the 13 cases with subendocardial infarction, the eosinophil count dropped to 20 or below for an average of 1.7 days and stayed at 50 per cent below estimated normal for an average of 3.3 days, two days less than the previous group. In the four cases with acute congestive failure, an eosinopenia developed on the second day, but the counts promptly rose to a high level on the third or fourth day. It appeared that the number of days of eosinopenia roughly paralleled clinical signs of difficulty, such as congestive failure, fever, and continued pain. The data suggest also that in cases of suspected myocardial infarction associated with equivocal electrocardiographic findings, the serial eosinophil count may be of value as an adjunct in diagnosis. Furthermore, in proved instances of myocardial infarction,

the eosinophil count may aid in determining the extent of muscle destruction.

WENDKOS

Leaf, A., and Mamby, A. R.: An Antidiuretic Mechanism not Regulated by Extracellular Fluid Tonicity. J. Clin. Investigation **31**: 60 (Jan.), 1952.

The preceding paper described an antidiuretic mechanism in normal man which tends to maintain effective serum solute concentration within narrow limits. To study the sustained low serum sodium concentrations in patients without intrinsic renal disease, the authors studied four patients with Addison's disease and eight patients with congestive heart failure.

It was shown that in inadequately treated Addison's disease, in certain cases of congestive failure who developed low serum sodium concentrations during treatment, and in normal dogs depleted of extracellular fluid electrolyte, an abnormality of water excretion exists. There is a dilution of serum with a concentrated urine and a failure of a prompt water diuresis following water administration. This pattern may be reduplicated by the continuous action of small amounts of posterior pituitary extract.

Apparently the mechanism which the normal subject uses to correct an extracellular deficit is grossly exaggerated to overexpand extracellular fluid volume by the edematous cardiac subject. This indicates that it is not a change in total extracellular volume but more likely insufficiency of some critical portion, probably intravascular, which sets off this volume-expanding antidiuretic mechanism. It is believed that this abnormal antidiuretic pattern represents a continued activity of the supraopticohypophyseal antidiuretic system in the presence of a dilute extracellular fluid which normally would inhibit this activity.

WAIFE

Strauss, M. B., Davis, R. K., Rosenbaum, J. D., and Rossmeisl, E. C.: Production of Increased Renal Sodium Excretion by the Hypotonic Expansion of Extracellular Fluid Volume in Recumbent Subjects. J. Clin. Investigation **31**: 80 (Jan.), 1952.

The authors describe experiments in which the volume of extracellular water was expanded at the same time that the concentrations of sodium and chloride were reduced. It was found that hypotonic expansion of extracellular fluid volume in the recumbent position leads to an increased urinary excretion of sodium, although the load presented to the tubules is actually diminished. In short, there was diminished tubular reabsorption of sodium. This did not occur in the seated subjects, suggesting that the locus of action is in the cephalad portion of the body. A hypothesis is suggested that the converses of these observations also hold; namely contraction of extracellular volume in the cephalad portion of the body may be a stimulus for sodium retention.

WAIFE

Leaf, A., and Mamby, A. R.: The Normal Antidiuretic Mechanism in Man and Dog; Its Regulation by Extracellular Fluid Tonicity. J. Clin. Investigation **31**: 54 (Jan.), 1952.

The total concentration of solutes in serum and urine of normal male adults and normal dogs was determined by a new freezing point method. Water deprivation was found to cause a slight rise in total solute concentration of the serum together with a maximal concentration of the urine. After water administration, a slight but measurable dilution of the serum occurred. With this, the urine became progressively more dilute, reaching hypotonic levels.

In the dog, antidiuretic activity of the serum was demonstrable at the end of the water deprivation period, but no activity was found during water diuresis. Antidiuretic activity was measured by a serum assay method using four posthypophysectomized rats.

The normal diuretic reaction may be explained as follows: As a result of restricted fluid intake and continued insensible loss of water, there results a slight increase in total solute concentration of the serum and extracellular fluid. Through osmoreceptors there is an outpouring of antidiuretic hormone. This in turn acts upon the renal tubule cells to produce increased reabsorption of water from glomerular filtrate with a resultant formation of concentrated urine and conservation of body water. Following water administration, the dilution of extracellular fluid inhibits posterior pituitary activity, leading to a state of functional diabetes insipidus, which permits diuresis of a dilute urine, thus ridding the body of the excess water. These mechanisms seem ideally designed to preserve the total effective solute concentration of the serum within narrow limits.

WAIFE

Lenzi, F., and Caniggia, A.: Potassium Intoxication in a Patient with Diabetic Coma. Cardiologia **19**: 265, 1951.

A case with diabetic coma and hyperpotassemia is reported. Intravenous injection of 20 cc. of 5 per cent potassium chloride was followed by hyperpotassemia. The electrocardiogram showed the following modifications: depression of S-T and inversion of the T; then intraventricular conduction disturbances; and later, ventricular fibrillation. Sinus rhythm with marked bradycardia returned later, and a monophasic contour of the QRS-T was noted at that time. The author finds a close similarity between these electrocardiographic changes and those observed in the turtle after experimental hyperpotassemia.

The literature concerning the mechanism of hyper-

potassemic changes of the electrocardiogram is reviewed. The author believes that the electrical potentials of the cells are mostly affected by modifications of the relationships between the concentration of potassium in the extra- and intracellular compartments (modifications of the K-surface gradient).

LUISADA

Deane, N., Ziff, M., and Smith, H. W.: The Distribution of Total Body Chloride in Man. J. Clin. Investigation **31**: 200 (Feb.), 1952.

The total body chloride was determined in seven non-edematous subjects. Total body water and extracellular fluid volume were determined by the antipyrine and sucrose methods as described previously. The dilution of sodium bromide was used to determine total chloride distribution.

Total chloride averaged 30.1 mEq. per kilogram body weight; intracellular chloride averaged 29.7 per cent of total chloride. The data show that the intracellular fraction ranges from about 20 to 40 per cent of the total chloride, and it would seem that a change in total chloride does not necessarily represent the change in volume of extracellular fluid.

It would appear that intracellular chloride is highly variable in amounts, and calculations of changes of extracellular fluid volume, based on changes in total body chloride, must have an uncertain value.

WAIFE

Peschel, E., and Lohmann-Peschel, R.: Electrolyte Metabolism During Rice Diet. Arch. Int. Med. **89**: 234 (Feb.), 1952.

A survey is given of the serum electrolyte pattern of patients on strict rice diet. A moderate drop in chloride and, correspondingly, an increase in bicarbonate occur; both develop during the first weeks of the treatment. Sodium, potassium, and total ionic concentrations are essentially maintained.

The strict rice diet can be given without danger of serum electrolyte disturbance to all patients with cardiac decompensation and to 95 per cent of those with good renal function. Difficulties have to be expected in patients with severe primary or secondary renal impairment, and they might arise in 5 per cent of those in whom urinary findings and results of renal-function tests seem to indicate a disturbed renal regulatory function.

BERNSTEIN

Luisada, A. A., and Contro, S.: On the Time Relationship of the Waves of the Ballistocardiogram. Acta cardiol. **6**: 847, 1951.

A graphic study of the ballistocardiographic waves was made. The ballistocardiogram was recorded by a photoelectric method, and the sensitivity of the apparatus was increased by adding an amplifier. Various technical causes of error of this method were noted. Instructions for its use are given.

The main observations were made in a series of eight normal young adults. Additional studies were made in subjects with complete A-V block, auricular fibrillation, and gallop rhythm.

A comparison was made between the ballistocardiographic waves and those of (a) the phonocardiogram, (b) the phlebogram, (c) the pneumocardiogram, (d) the apex cardiogram, (e) the arterial tracings of the suprasternal notch and the carotid arteries, and (f) the arterial tracings of the abdominal aorta, and of the femoral, tibial and pedial arteries. The various time relationships are observed and discussed.

While the main interpretation of the origin of the ballistocardiographic waves is confirmed, various points concerning the waves taking place during ventricular diastole should be corrected.

LUISADA

Thompson, D. D., and Pitts, R. F.: Effects of Alterations of Renal Arterial Pressure on Sodium and Water Excretion. Am. J. Physiol. **168**: 490 (Feb.), 1952.

When glomerular filtration rate was reduced by inflating a balloon in the descending aorta above the renal arteries, sodium and water excretion were reduced. The percentage of sodium reabsorbed of that which was filtered, was increased when the glomerular filtration rate was reduced. Results were qualitatively similar after adrenalectomy, section of the pituitary stalk, or sympathetic renal denervation. It is considered that these results indicate that decreased glomerular filtration rate promotes fluid retention.

OPPENHEIMER

Smedal, H. A.: Air Transportation of Persons with Cardiorespiratory Disease and/or Injury. J. Aviation Med. **23**: 33 (Feb.), 1952.

This discussion is largely of a theoretic nature. It is seen that persons with coronary heart disease tolerate anoxia of a moderate degree very well. One should therefore be able to be quite liberal in one's advice to coronary disease patients in regard to their travel by air. With the advent of the extensive use of pressurized cabins much of the hazard of patients with cardiorespiratory disease or injury has been diminished and even eliminated.

The chief hazard which remains is that of explosive decompression. Since the difficulty with this is mainly sudden anoxia, this danger can be a real one to individuals with cardiorespiratory disease. It must be remembered that these individuals must be protected by having an adequate source of supplemental oxygen readily available.

It seems, therefore, that there are very few people with cardiorespiratory disease who cannot be trans-

ported by air. Precautions must be taken so that the patients do not become anxious, frightened, tired, or motion sick or anoxic. With adequate care and preparation most of these patients may be transported by air.

BERNSTEIN

Ritter, E. R.: Pressure-Flow Relations in the Kidney. Alleged Effects of Pulse Pressure. Am. J. Physiol. **168:** 480 (Feb.), 1952.

A dog's kidneys were perfused in situ by a system which permitted mean arterial and pulse pressures to be varied independently. The rates of arterial inflow were measured. Changes in pulse pressure of themselves had no effect on renal blood flow. Abrupt changes in arterial pressure produce prolonged variations in the resistance of renal vessels. These are not due to pulse pressure changes. When renal resistance is calculated (with corrections for "yield" pressure) it decreases when arterial pressure is lowered to 80 mm. Hg. The resistance falls to a minimum when arterial pressure falls to 65 mm. Hg and then remains about constant.

The author does not regard the arterial pressure at which flow ceases as a practical indicator of renal vascular resistance. He concludes that active changes in the afferent arterioles produced the changes in renal resistance found in these experiments.

OPPENHEIMER

Iseri, L. T., Batchelor, T. M., Boyle, A. J., and Myers, G. B.: Studies of Fluid, Electrolyte, and Nitrogen Balance in Acute Renal Insufficiency. Arch. Int. Med. **89:** 188 (Feb.), 1952.

Metabolic balances of water, potassium, chloride, and nitrogen were determined in five cases of severe acute renal insufficiency for periods of 6 to 23 days; extracellular and intracellular partition of water was calculated from chloride balance. Serial determinations of glomerular filtration rate, renal plasma flow, tubular mass, and sodium and water reabsorption were made in four patients. Hyponatremia and hypochloremia developed consistently during the oliguric phase of lower nephron nephrosis. Hyperkalemia developed toward the end of the first week of oliguria in one patient. A regimen containing little or no protein and as much dextrose as possible prevented hyperkalemia in the remaining patients and slowed the rise in blood nonprotein nitrogen concentration.

During the diuretic phase, plasma sodium and chloride levels were subject to considerable fluctuation, depending upon (1) the relative external losses of electrolyte and water, (2) the proportionate intakes of electrolyte and water, and (3) concurrent internal shifts. Greater impairment in reabsorptive capacity for water than for electrolyte led to dehydration with elevation of plasma concentrations. These observations indicated that as long as polyuria persists and renal homeostasis of electrolyte is impaired, it is necessary to control the proportion of electrolyte to water in the diet, preferably in accordance with plasma and urinary concentrations.

During the diuretic stage, potassium intakes of 100 mEq. or more per day were necessary to restore normal plasma levels in these patients.

BERNSTEIN

Birnbaum, G. L.: Simple Cardiac Defibrillator. J. Thoracic Surg. **23:** 183 (Feb.), 1952.

A simple portable and inexpensive defibrillator is described. The parts are readily available and can be easily assembled. The apparatus utilizes 110 volt alternating house current and is designed for use in cases of ventricular fibrillation associated with cardiac arrest occurring in the operating room.

Preceding the application of the electrodes to the heart, 5 cc. of 1 or 2 per cent procaine is injected into the cavity of the right auricle or ventricle, and the heart is massaged in order to distribute the drug through the coronary circulation. The defibrillator electrodes are then placed in contact with each side of the heart, as far apart as possible, and 1 to 1.5 amperes of current are sent through the organ for approximately one fifth of a second. If fibrillation persists after two electric shocks, no more procaine is used, but massage is continued and shock may be tried a few more times.

ABRAMSON

Ryan, J. M., and Hickam, J. G.: The Alveolar-Arterial Oxygen Pressure Gradient in Anemia. J. Clin. Investigation **31:** 188 (Feb.), 1952.

Despite equivalent alveolar ventilation, the arterial blood oxygen tension is significantly lower in the anemic than in the nonanemic control group, and the mean difference between alveolar and arterial oxygen tension (A-A gradient) is significantly greater in the anemic group. There was a significant negative correlation between hemoglobin concentration and the A-A gradient. During the inspiration of a reduced oxygen mixture (14.7 per cent oxygen), the increased gradient in anemic patients may be explained by venous admixture rather than by impairment of alveolar-capillary diffusion, such as might be caused by pulmonary edema. Venous admixture to oxygenated blood may occur through the Thebesian veins and bronchial veins, or blood flow through poorly aerated lung, and some oxygen may be lost from the blood in the left ventricular cavity from diffusion across the endocardium into left ventricular muscle.

WAIFE

Deane, N., and Smith, H. W.: The Distribution of Sodium and Potassium in Man. J. Clin. Investigation **31:** 197 (Feb.), 1952.

By means of the isotope dilution technic, simultaneous measurements of body water distribution and total body electrolytes were made in man. Total body water was determined by antipyrine

dilution method; extracellular fluid was measured by the calibrated infusion technique of measuring the maximal volume of distribution of sucrose. Intracellular water was calculated as a difference between the antipyrine and sucrose volumes. The difference between body weight and weight of the sucrose volume was accepted to be cellular mass. Radioactive sodium and radioactive potassium were used.

The average value for intracellular potassium was found to be 112 mEq. per liter (with a range of 96 to 125) of intracellular water; 49 mEq. per kilogram of cellular mass; and 87 mEq. per kilogram of body solid.

Intracellular sodium averaged 37.0 mEq. per liter of intracellular water, with a range of 31.3 to 43.5; 17.6 mEq. per kilogram of cellular mass; and 35.7 mEq. per kilogram of body solid. These values are in close agreement with comparable data obtained from studies in the dog and are averaged concentrations representing all the tissues in the body.

WAIFE

Dressler, W.: Effort Syncope as an Early Manifestation of Primary Pulmonary Hypertension. Am. J. M. Sc. **223:** 131 (Feb.), 1952.

Cyanosis has been considered the hallmark of primary pulmonary arterial hypertension and sclerosis. The author believes that this view should be abandoned because cyanosis was not observed until two to five years after the onset of symptoms in his cases, and only became severe terminally. The cases he observed and six cases selected from the literature showed certain common features: (1) effort syncope, (2) right ventricular hypertrophy without apparent cause, (3) pulmonary artery dilation without an increase in bronchovascular markings, and (4) accentuation of the second pulmonic sound. Effort syncope may be observed in three forms of heart disease: aortic stenosis, congenital venoarterial shunt, and heart block. If these are excluded and certain of the aforementioned signs are present, primary pulmonary vascular disease may be suspected.

The cause of effort syncope in these cases is not understood. It may arise as a vasovagal reflex originating in the neuroreceptors within the wall of the pulmonary artery. This reflex produces a fall in blood pressure and a slowing of heart beat. Effort syncope is not an invariable finding in these cases, but when present, may be a useful diagnostic sign.

SHUMAN

Hutt, M. P.: Effect of Disease on Erythrocyte and Plasma Potassium Concentrations. Am. J. M. Sc. **223:** 176 (Feb.), 1952.

The red blood cell potassium concentration was determined by obtaining the values for whole blood and plasma potassium together with the hematocrit. In 14 normal subjects, the average erythrocyte concentration was 94.5 mEq. per liter and the plasma concentration was 4.4 mEq. per liter. The presence of anemia did not appear to influence the potassium concentrations.

In a group of patients with disturbances in potassium metabolism, it was found that the plasma concentration may not reflect the intracellular potassium stores as measured in the red cells. Increased plasma potassium with low or normal cellular levels was not uncommon especially in renal failure with vomiting and poor dietary intake. The administration of potassium may be associated with a more rapid rise in cellular potassium than is reflected in the plasma potassium levels. A close correlation between the changes in the cell and plasma was not always observed. The erythrocyte potassium level appears to reflect changes in body stores of this cation, and may have important implications in treatment of patients with disturbed potassium metabolism.

SHUMAN

BOOK REVIEWS

Notions Cardiologiques Nouvelles. *C. Lian, and P. Danset.* Paris, Masson et Cie., 1951. 214 pages, 39 figures. 800 fr.

In this monograph the senior author, a well known contributor in this field, avowedly limits his subject matter to those aspects of cardiology which have been the objects of his personal research. This, then, is primarily a review of Lian's contributions to cardiology. In general the chapters are unrelated and represent short summaries on a variety of subjects.

There is consistent emphasis on the physiologic concepts in cardiology and the dynamics of mitral stenosis and left ventricular failure are well discussed. Perhaps the best presentations are those concerned with the clinical diagnosis of mitral stenosis and the summary on present day handling of the patients with patent ductus arteriosus and tetralogy of Fallot. Another part of considerable interest stresses the importance of listening for murmurs and rubs in the back in cardiac patients. The authors' ideas on digitalis therapy differ from those currently practiced in this country, and it is particularly unfortunate that they misquote the Anglo-American technic of digitalization, stressing that it is uniformly carried to the point of digitalis toxicity as evidenced by nausea, vomiting or a very slow pulse, and only at this point is it considered adequate. There are several other points of difference between the authors' concepts and those favored in this country; for example, the notion that a presystolic gallop is always evidence of cardiac failure (a protodiastolic gallop is not associated by the authors with failure), and that short, intermittent courses of Digitaline Nativelle are the best treatment of cardiac failure.

It is regrettable that the authors' emphasis on certain references—and the great majority are those of the senior author—results in misconceptions, particularly as regards priority of publication in specific instances. Perhaps the most flagrant of these is a failure to acknowledge Sweet as the originator of the idea of pulmonary vein–azygos vein anastamosis in mitral stenosis. The Blalock-Taussig operation and the inferior vena cava ligation of Cossio on the other hand are properly credited. In summary, it could be said that this monograph is an interesting compilation of the senior physician's concepts and contributions to cardiology.

M. Irené Ferrer

Angiocardiography. Annals of Roentgenology. Vol. XX. *Charles T. Dotter, and Israel Steinberg.* New York, Paul B. Hoeber, 1951. 304 pages, 635 illustrations on 252 figures. $16.00.

This attractive volume on angiocardiography is volume XX in the Annals of Roentgenology, and one of the best in the series. It is carefully written, well illustrated and covers the subject thoroughly. The authors are experts in this field, but fortunately not in this narrow subspecialty alone. They are, therefore, able adequately to evaluate the relative importance of angiocardiography, ordinary radiographic and fluoroscopic methods, and cardiac catheterization in establishing reasonably correct diagnoses in patients with heart disease.

The book starts with a full and complete discussion and description of technic, equipment, contrast substances, and the dangers of the method. There follows naturally a full description and illustrations of the normal heart and great vessels, taking each chamber and vessel in turn. Subsequent chapters cover the various types of acquired and congenital heart disease, then follow interesting chapters on mediastinal and pulmonary tumors, and various types of pulmonary disease, as it affects the pulmonary circulation. The only thing lacking is adequate discussion and illustration of direct aortography and retrograde aortography, both apparently outside the field of the authors' experience.

The monograph is very well printed, on excellent paper, and is profusely illustrated, almost entirely from the authors' own material. There are 635 illustrations in 252 figures, with line drawings adequately explaining the accompanying roentgenograms. One marvels that such excellent material could be collected and accurately annotated in the relatively short period since the method was devised. It is a tribute to hard work and intense concentration in a small field where cardiology and roentgenology overlap.

On the whole it is an excellent monograph on angiocardiography, the only complete and authoritative one at present in the English language, and a "must" book for cardiologists and roentgenologists, whether they are doing angiocardiography or not.

Merrill C. Sosman

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7–9170

1953 HEART FUND

The goal for the 1953 Heart Fund Campaign of the Association and its affiliates has been set at $10,000,000. The Campaign will be conducted throughout the month of February. Funds raised will be used for the national program of scientific research, professional and lay education, and the furtherance of community service programs. Over $6,560,000 was raised nationally, in 1952, to support these aims.

"Help Your Heart Fund—Help Your Heart," is the new slogan for the 1953 Heart Fund. American Heart Week, including St. Valentine's Day, has been set for February 8–14.

Physicians are rendering increasingly valuable support to the Heart Fund Campaign by taking active part in their community programs. They serve as speakers and committee members, and help to inform the public on the progress being made in the treatment and care of heart patients. Many physicians give assistance in clinics, symposia, and meetings devoted to the cardiovascular diseases, which are sponsored by the Association and its affiliates.

AMERICAN COLLEGE OF PHYSICIANS

The annual meeting of the American College of Physicians will be held in Atlantic City, April 13–17, at Convention Hall, immediately following the annual meeting of the American Heart Association. Further information may be obtained by writing the executive secretary, Mr. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

ANNUAL MEETING RESERVATIONS

All those planning to attend the Association's Annual Meeting and Scientific Sessions at the Hotel Chelsea, Atlantic City, April 8–12, may obtain hotel reservation forms from the Association. Reservations should then be mailed *directly* to the hotel in Atlantic City at the earliest possible date. The same hotel reservation form may be used by those desiring to attend the meetings of both the American Heart Association and the American College of Physicians.

"HEART DISEASE IN CHILDREN"

The Association and its affiliated Heart Associations throughout the country have begun distribution of a new booklet, "Heart Disease in Children." This booklet presents an up-to-date summary of the information now available on the prevention and treatment of rheumatic fever, the treatment of rheumatic heart disease, and the correction of congenital heart defects.

The booklet is intended for parents, teachers, and all others concerned with the health and care of cardiac children. It is recommended to physicians to use with parents of patients, and with the patients themselves.

The booklet may be obtained from affiliated Heart Associations or from the American Heart Association at 44 East 23rd Street, New York 10, N. Y.

MEDICAL FELLOWSHIPS

Fellowships and scholarships available through National Medical Fellowships, Inc., are offered to Negro candidates in all the fields of medicine. Applicants are expected to devote all their time to their studies. Applications must be filed by March 1, 1953. They may be secured by writing to Mrs. Hilde Reitzes, Fellowship Secretary, National Medical Fellowships, Inc., 951 East 58th Street, Chicago 37, Ill.

ASSEMBLY PANELS FOR ANNUAL MEETING

The following have been appointed as Chairmen to lead Panel Discussions at the annual meeting of the Assembly in Atlantic City, N. J., on Wednesday, April 8, 1953:

Panel I. Education: Lay.....George N. Aagaard, M.D., Dallas

Panel II. Education: Professional.....John Talbott, M.D., Buffalo

Panel III. COMMUNITY SERVICE: RHEUMATIC FEVER PROGRAMS.....David D. Rutstein, M.D., Boston, and George M. Wheatley, M.D., New York City

Panel IV. COMMUNITY SERVICE: HOME CARE AND REHABILITATION.....Martin Cherkasky, M.D., New York City, and V. Thomas Austin, M.D., Urbana, Ill.

Panel V. RESEARCH.....Lowell A. Rantz, M.D., San Francisco, and Stanley E. Bradley, M.D., New York City

Panel VI. FUND RAISING.....Irving B. Hexter, Cleveland; Warren B. Cooksey, M.D., Detroit; and Donald G. Price, New York City

Panel VII. RELATIONSHIP OF NATIONAL, STATE, AND LOCAL HEART ASSOCIATIONS.....Paul V. Ledbetter, M.D., Houston; Frank N. Isbey, Detroit; and M. Linwood Beck, Atlanta

The Assembly Planning Committee of the American Heart Association is under the chairmanship of William H. Bunn, M.D., of Youngstown, Ohio.

FIRST EUROPEAN CONGRESS OF CARDIOLOGY

The first European Congress of Cardiology was held in London from September 9 to 12, 1952, under the auspices of the British Cardiac Society. Sir John Parkinson, President of the Society, was Chairman of the Congress. In addition to 490 European members from twenty-one countries, twenty members from the United States were present.

A feature of the Scientific Sessions was a symposium on the surgical treatment of mitral stenosis.

Dr. Maurice Campbell sketched the history of mitral valvotomy from the earliest attempts twenty-five years ago to the achievement by Mr. R. C. Brock in 1950. Dr. Campbell described the indications for operation and results in 100 cases. The widespread acceptance and success of this procedure was demonstrated by the substantial series described by Professor Soulié, Dr. Werkö, Professor Froment and Dr. Santy from the Continent, Mr. Holmes Sellors and Dr. Swan from England, and by Dr. J. F. O'Neill of the United States, who reported on 800 operations.

Dr. Campbell's judgment was shared by many speakers. He said the operation should be considered for all patients with mitral stenosis who are progressively disabled, especially young patients with evidence of pulmonary congestion, orthopnea, cardiac asthma and recurrent pulmonary edema. Conditions which rendered the operation less likely to give outstanding results but which did not preclude a good result, were auricular fibrillation, calcification of the valve, associated aortic valve disease and moderate mitral regurgitation.

Another theme of interest was dealt with by Dr. Irving S. Wright, president of the American Heart Association, who reported the results of the study of the effect of anticoagulants on the mortality and morbidity of myocardial infarction in 1,031 cases. There was a reduction in the death rate of one-third, and in the rate for thromboembolic complication of four-fifths. Several confirmatory reports were presented in the discussion. There was no unanimity of agreement as to whether they should be used in every case. There was general interest in the use of Tromexan and other newer preparations.

ELECTROCARDIOGRAPHIC INTERPRETATION

A course in Electrocardiographic Interpretation for graduate physicians will be given at the Michael Reese Hospital by Louis N. Katz, M.D., Director of the Cardiovascular Department, Medical Research Institute, and associates. The class will meet each Wednesday from 7:00 to 9:00 p.m. for 12 weeks, beginning February 11. Further information and a copy of the lecture schedule may be obtained upon application to Mrs. Rivian H. Lewin, Administrative Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Ill.

MEETINGS

Jan. 30: Southern Section, American Federation for Clinical Research, Jung Hotel, New Orleans. Chairman, Dr. Albert Segaloff, Alton Ochsner Medical Foundation, 3503 Prytania Street, New Orleans.

Jan. 30–31: Western Society for Clinical Research, Sixth Annual Meeting, Carmel, Calif. Dr. Herbert N. Hultgren, Secretary, Stanford Hospital, San Francisco 15.

Feb. 9: New England Cardiovascular Society, John Hancock Hall, 180 Berkeley Street, Boston. Drs. Herrmann L. Blumgart and Robert W. Wilkins will conduct the meeting.

Apr. 8–12: Twenty-Ninth Annual Meeting, American Heart Association, Hotel Chelsea, Atlantic City, N. J.

Apr. 8–9: Assembly panels, Assembly meeting, meeting of the Scientific Council.

Apr. 10–12: Twenty-Sixth Scientific Sessions, American Heart Association, Hotel Chelsea, Atlantic City, N. J.

Apr. 13–17: American College of Physicians, 34th Annual Meeting, Hotel Chelsea, Atlantic City, N. J.

May. 7–10: National Congress of Cardiology, Sevilla, Spain. Secretary, Dr. E. Benot, 3 Paseo de las Delicias, Sevilla, Spain.